PB81-117822

Ambient Water Quality Criteria for Silver

(U.S.) Environmental Protection Agency
Washington, DC

Oct 80

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-071
October 1980

PB81-117822

Ambient Water Quality Criteria for Silver

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO.

2.

3. RECIPIENT'S ACCESSION NO.
PB81 117822

4. TITLE AND SUBTITLE
Ambient Water Quality Criteria for:
Silver

5. REPORT DATE
October, 1980

6. PERFORMING ORGANIZATION CODE
NTISEPAOWP

7. AUTHOR(S)
Environmental Criteria and Assessment Office

8. PERFORMING ORGANIZATION REPORT NO.
EPA-440/5-80-071

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Office of Water Regulations and Standards
Criteria and Standards Division
U.S. Environmental Protection Agency
Washington, D.C. 20460

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES
Supersedes draft document PB 292 441

16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Silver. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT
For Public Release

19. SECURITY CLASS *(This Report)*
Unclassified

20. SECURITY CLASS *(This page)*
Unclassified

21. NO. OF PAGES

22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

AMBIENT WATER QUALITY CRITERIA FOR
SILVER

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

DISCLAIMER

This report has been reviewed by the Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AVAILABILITY NOTICE

This document is available to the public through the National Technical Information Service, (NTIS), Springfield, Virginia 22161.

FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

ACKNOWLEDGEMENTS

Aquatic Life Toxicology

William A. Brungs, ERL-Narragansett
U.S. Environmental Protection Agency

David J. Hansen, ERL-Gulf Breeze
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects

Bonnie Carson (author)
Midwest Research Institute

Christopher DeRosa (doc. mgr.), ECAO-Cin
U.S. Enviromental Protection Agency

Bonnie Smith (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Ernest Foulkes
University of Cincinnati

Dinko Kello
Institute for Medical Research

Edward W. Lawless
Midwest Research Institute

Jerry F. Stara, ECAO-Cin
U.S. Environmental Protection Agency

Robert M. Bruce, ECAO-RTP
U.S. Environmental Protection Agency

Richard Bull, HERL
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Alfred Garvin
University of Cincinnati

Terri Laird, ECAO-Cin
U.S. Environmental Protection Agency

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, P. Gray, B. Gardiner, R. Swantack.

TABLE OF CONTENTS

Page

Criteria Summary

Introduction A-1

Aquatic Life Toxicology B-1
- Introduction
- Effects B-3
  - Acute Toxicity B-3
  - Chronic Toxicity B-6
  - Plant Effects B-10
  - Residues B-11
  - Miscellaneous B-11
  - Summary B-12
- Criteria B-13
- References B-34

Mammalian Toxicology and Human Health Effects

- Introduction C-1
- Exposure C-1
  - Ingestion from Water C-1
  - Ingestion from Food C-17
  - Inhalation C-21
  - Dermal C-29
- Pharmacokinetics C-33
  - Absorption C-33
  - Distribution C-40
  - Metabolism C-52
  - Excretion C-56
- Effects C-68
  - Acute, Subacute and Chronic Toxicity C-68
  - Synergism and/or Antagonism C 94
  - Teratogenicity C-102
  - Mutagenicity C-104
  - Carcinogenicity C-106
- Criterion Formulation C-116
  - Existing Guidelines and Standards C-116
  - Current Levels of Exposure C-119
  - Special Groups at Risk C-121
  - Basis and Derivation of Criterion C-122
- References C-129

CRITERIA DOCUMENT

SILVER

CRITERIA

Aquatic Life

For freshwater aquatic life the concentration (in µg/l) of total recoverable silver should not exceed the numerical value given by $e^{(1.72[\ln(\text{hardness})]-6.52)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$, the concentration of total recoverable silver should not exceed 1.2, 4.1, and 13 µg/l, respectively, at any time. The available data indicate that chronic toxicity to freshwater aquatic life may occur at concentrations as low as 0.12 µg/l.

For saltwater aquatic life the concentration of total recoverable silver should not exceed 2.3 µg/l at any time. No data are available concerning the chronic toxicity of silver to sensitive saltwater aquatic life.

Human Health

The ambient water quality criterion for silver is recommended to be identical to the existing water standard which is 50 µg/l. Analysis of the toxic effects data resulted in a calculated level which is protective of human health against the ingestion of contaminated water and contaminated aquatic organisms. The calculated value is comparable to the present standard. For this reason a selective criterion based on exposure solely from consumption of 6.5 grams of aquatic organisms was not derived.

INTRODUCTION

Silver is a white, ductile metal occurring naturally in the pure form and in ores. Principal uses of silver are in photographic materials, electroplating, as a conductor, in dental alloys, solder and brazing alloys, paints, jewelry, silverware, coinage, and mirror production. Silver is of some use as an antibacterial agent and has been shown to be bactericidal even in concentrations that are not great enough to precipitate proteins; the assumption is that silver is capable of interfering with essential metabolic processes in the bacterial cell (Goodman and Gilman, 1975).

Silver can exist in two valence states, Ag^+ and Ag^{++}. It has an atomic weight of 107.87. Solubilities of a few common silver salts in water are: AgCl, 1,930 µg/l; $AgNO_3$, 2.5×10^9 µg/l; and AgI, 30 µg/l (Windholz, 1976). Silver occurs primarily in the form of the sulfide (argentite Ag_2S) or intimately associated with other metal sulfides, especially those of lead and copper. Other common silver minerals include cerargyrite (AgCl), proustite ($3AgS\ As_2S_3$), pyragyrite ($3Ag_2S\ Sb_2S_3$), stephanite ($5Ag_2S\ Sb_2S_3$) and native metallic silver. Most lead and copper ores are argentiferous, though there are important exceptions. Recovery of silver and gold from these ores constitutes an important part of their metallurgical treatment.

Silver is also commonly associated in nature with gold. Not only does gold occur with silver in copper and lead ores, but native metallic gold usually contains silver. Gold and silver are mutually soluble in each other in all proportions in the metallic state.

Silver is usually found in extremely low concentrations in the aquatic environment, due both to its low crustal abundance and the effectiveness of controls on its mobility in water. In a study of 10 U.S. rivers, Kharkar, et al. (1968) detected silver in concentrations ranging from 0.092 to 0.55 µg/l. Hem (1970) cites studies of public drinking water supplies and river waters which report median concentrations of 0.23 and 0.09 µg/l, respectively. The geochemistry of silver has been extensively reviewed by Boyle (1968).

Sorption and precipitation processes are effective in reducing the concentration of dissolved silver and result in higher concentrations in the bed sediments than in the overlying waters. Sorption by manganese dioxide and precipitation with halides are probably the dominant controls on the mobility of silver in the aquatic environment. Some silver is also bioaccumulated, and the remainder is transported in solution to the oceans (U.S. EPA, 1979).

REFERENCES

Boyle, R.W. 1968. The geochemistry of silver and its deposits. Geol. Survey of Canada, Bull. 160, Ottawa, Canada.

Goodman, L.S. and A. Gilman (eds.) 1975. The Pharmacological Basis of Therapeutics. 5th ed. MacMillan Publishing Co., Inc., New York.

Hem, J.D. 1970. Study and interpretation of the chemical characteristics of natural waters. U.S. Geol. Survey Paper 1473, Washington, D.C. p. 202.

Kharkar, D.P., et al. 1968. Stream supply of dissolved silver, molybdenum, antimony, selenium, chromium, cobalt, rabidium and cesium to the oceans. Geochim. Cosmochim. Acta. 32: 285.

U.S. EPA. 1979. Water-related environmental fate of 129 priority pollutants. EPA 68-01-3852. U.S. Environ. Prot. Agency, Washington, D.C.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed. Merck and Co., Inc., Rahway, New Jersey.

Aquatic Life Toxicology*

INTRODUCTION

Silver exhibits oxidation states of 0, +1, +2, and +3, but only the 0 and +1 states occur to any extent in the environment. In natural water, the monovalent species is the form of environmental concern. In water, silver may exist as simple hydrated monovalent ions completely dissociated from anions that at one time could have been part of its crystalline salt lattice. In addition, monovalent silver ions may exist in various degrees of association with a large number of inorganic ions, such as sulfate, bicarbonate, and nitrate, to form numerous compounds with a range of solubilities and potentials for hydrolysis or other reactions. Hem (1970) speculates that where chloride concentrations exceed 35 mg/l, silver chloride may exert a major control on solubility of silver.

Sorption appears to be the dominant process leading to partitioning into sediments. It appears that manganese dioxide, ferric compounds, and clay minerals all have some degree of adsorptive affinity for silver and are involved in its deposition into sediments (Kharkar, et al. 1968). Dyck (1968) observed that sorption of silver was strongly dependent on pH. In addition, silver may be freed from these compounds by reducing conditions in the sedimentary layer and thus may be reduced to metallic silver or may combine with reduced sulfur to form the extremely insoluble silver sulfide. Finally silver may exist as metal-organic complexes or may be adsorbed by organic materials in natural waters.

---

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Silver is one of the most toxic metals to freshwater aquatic life. Most of the toxicity studies have been conducted with silver nitrate, which is an excellent source of free soluble silver ions. Insoluble silver salts are much less toxic than silver nitrate. Chambers and Proctor (1960) found that the germicidal action of silver in distilled water was related to the concentration of silver ions rather than the physical nature of the silver from which the ions were originally derived.

Limited information is available concerning the relationship of various forms of silver and toxicity to aquatic animals. Data indicate that the acute toxicity of silver to freshwater fishes and Daphnia magna is related to water hardness, with silver being more toxic in soft water. The acute toxicity of silver also is related to chloride concentration, but the data base for this relationship is insufficient to develop criteria on the basis of chloride concentration. The data base for saltwater organisms is insufficient to determine the importance of salinity, temperature, and other water quality factors on the toxicity of silver.

Of the analytical measurements currently available, a water quality criterion for silver is probably best stated in terms of total recoverable silver, because of the variety of forms of silver that exist in bodies of water and the various chemical and toxicological properties of these forms. The forms of silver that are commonly found in bodies of water and are not measured by the total recoverable procedure, such as the silver that is in minerals, clays, and sand, probably are forms that are less toxic to aquatic life and probably will not be converted to the more toxic forms very readily under natural conditions. On the other hand, forms of silver that are commonly found in bodies of water and are measured by the total recoverable procedure, such as the free ion and the hydroxide, carbonate, and sulfate salts, probably are forms that are more toxic to aquatic life or can be converted to the more toxic forms under natural conditions. Because the criterion is derived on the basis of tests conducted on soluble inorganic salts of silver, the total silver and total recoverable silver concentrations in the tests will probably be about the same, and a variety of analytical procedures will produce about the same results. Except as noted, all concentrations reported herein are expected to be essentially equivalent to total recoverable silver concentrations. All concentrations are expressed as silver, not as the compound.

EFFECTS

Acute Toxicity

The data base concerning acute toxicity of silver to freshwater organisms includes 82 acute values for 10 species from nine different taxonomic families (Table 1). The invertebrate species include a planktonic crustacean, a benthic crustacean that is a detritivor, and a benthic insect among others, whereas the fish species include a salmonid and five nonsalmonid species.

For the four invertebrate species, the acute values for silver range from 0.25 µg/l for *Daphnia magna* to 4,500 µg/l for the scud *Gammarus pseudolimnaeus*, both of which were tested in Lake Superior water (Table 1).

Most of the acute values for freshwater fish are for the rainbow trout and fathead minnow (Table 1). The acute values in flow-through tests ranged from 3.9 µg/l for the fathead minnow in soft water to 280 µg/l for rainbow trout in hard water. This range of acute values for six fish species was much less than the range of acute values for four invertebrate species.

Chapman, et al. (Manuscript) examined the acute toxicity of silver to *Daphnia magna* with and without food being added to the test solutions. The acute value with food was 9.5 µg/l (Table 6). In a side-by-side test conducted with no food added (Table 1), the acute value was 0.25 µg/l. Lemke (Manuscript) also reported the results of side-by-side tests to compare the effect of food on acute toxicity. The result with added food was 43 µg/l (Table 6), and with no added food the results were 8.4 and 15 µg/l (Table 1). Because this effect is observed with some metals, but not with others, it appears that this daphnid food, or some component of it, greatly decreases the acute toxicity of silver.

The results of a study (EG&G Bionomics, 1979) designed to evaluate the relative toxicity of different forms of silver to the fathead minnow are given in Tables 1 and 6. Flow-through tests using measured total silver and free silver (pAg) concentrations were conducted. Silver nitrate with a 96-hour LC_{50} value of 16 µg/l (Table 1) was the most toxic silver compound. The 96-hour LC_{50} values for silver were 510 and 5,600 µg/l when the concentration of chloride was increased to 500 and 2,000 mg/l, respectively (Table 6). These test solutions were clear, indicating that silver was apparently present as a soluble chloride complex. Silver thiosulfate and both forms of silver sulfide were even less toxic.

The results of a round-robin test in which six laboratories each conducted duplicate static tests with Daphnia magna and duplicate static and flow-through tests with rainbow trout and fathead minnows (Lemke, Manuscript) are given in Table 1. The results of all except one test, were based on measured concentrations. Each laboratory reported that for the fathead minnow and rainbow trout the results of the flow-through tests were lower than the results of the static tests. The hardness of the water used in each laboratory was available, and so a least-squares regression was performed on the natural logarithms of the acute values (the flow-through values for the fish) on the natural logarithms of hardness. The resulting slopes were 2.29, 1.65, and 1.63 for Daphnia magna, rainbow trout, and fathead minnow, respectively, and all were statistically significant (p=0.01). The concentrations of chloride were 1.2, 32, 8, 11, 13, and 1 mg/l in the waters whose hardnesses were 48, 255, 54, 46, 38, and 75 mg/l, respectively. The regressions on chloride concentrations were not statistically significant (p=0.05).

Other data, however, do not show this amount of effect of hardness on the acute toxicity of silver. Goettl and Davies (1978) tested the acute toxicity of silver to the fathead minnow, speckled dace, and mottled sculpin in both soft and hard water. In addition, Davies, et al. (1978) tested the rainbow trout in soft and hard water. These tests produced slopes of 0.10, 0.50, 0.46, and 0.26, respectively. The last slope is not statistically significant (p=0.05), but the significance of the first three cannot be tested because only two points are available.

The apparent lack of effect of chloride is surprising, although the range of concentrations may be too low. The contradictory evidence concerning the effect of hardness on acute toxicity is also surprising. A comparison of all the available data concerning the acute toxicity of silver to both fathead minnows and rainbow trout suggests the possibility that silver was unusually toxic in the hard water used by Goettl and Davies (1978) and Davies, et al. (1978). Therefore, these results were not used in describing the effect of hardness on the acute toxicity of silver. For the remaining data, a least-squares regression of the natural logarithms of the acute values on the natural logarithms of hardness produced slopes of 2.35, 1.30, and 1.50, for Daphnia magna, rainbow trout, and fathead minnows, respectively. All three slopes were statistically significant (p=0.01). If the data for hard water from Goettl and Davies (1978) and Davies, et al. (1978) are used, the slopes for rainbow trout and fathead minnow change from 1.30 and 1.50 to 1.00 and 1.14, respectively.

The arithmetic mean slope (1.72) was used with the geometric mean toxicity value and hardness for each species to obtain a logarithmic intercept for each species, but again the data obtained in hard water by Goettl and Davies (1978) and Davies, et al. (1978) were not used. The species mean acute intercept, calculated as the exponential of the logarithmic intercept, was used to rank the relative sensitivities of the species (Table 3). A freshwater Final Acute Intercept of 0.00147 μg/l was obtained for silver using the species mean acute intercepts listed in Table 3 and the calculation procedures described in the Guidelines. Thus the Final Acute Equation is $e^{(1.72\ [\ln(\text{hardness})]-6.52)}$.

For saltwater animals, acute toxicity data are available for five fish and five invertebrate species. Fishes were both the most sensitive and most resistant species tested (Table 3), but invertebrate species as a group were generally more sensitive to silver than were the fish. Toxicity values ranged from 4.7 μg/l for the summer flounder to 1,400 μg/l for the sheepshead minnow. The Saltwater Final Acute Value for silver, derived from the species mean acute values listed in Table 3 using the calculation procedures described in the Guidelines, is 2.3 μg/l.

Chronic Toxicity

The results of Daphnia magna renewal life-cycle tests are given in Table 2. These chronic tests were conducted as part of a round-robin testing program, similar to that discussed in Lemke (Manuscript), to evaluate methods for acute and chronic toxicity tests using Daphnia magna (Nebeker, et al. Manuscript b). In contrast to the results of the acute tests, no relationship could be found between hardness and chronic toxicity. Three of the chronic values (2.6, 13, and 5.2 µg/l) are from the laboratory which reported acute values of 0.6 and 1.1 µg/l. In addition, a third acute in the same laboratory produced an acute value of 0.25 µg/l (Nebeker, et al. Manuscript a). The chronic values of 15 and 29 µg/l were from the same laboratory as the acute values of 15 and 8.4 µg/l, whereas the chronic value of 5.2 µg/l corresponds to the acute value of 0.64 µg/l. In each laboratory the average acute value for silver was lower than the average chronic value, probably because food was added to the test solutions in the chronic test, but not in the acute tests.

Special acute tests with Daphnia magna were conducted in two laboratories by adding food to the test solution as is done in the chronic test. In one laboratory the acute values were 8.4 and 15 µg/l without food (Table 1) and 43 µg/l with food (Table 6). The comparable chronic values were 15 and 29 µg/l, which results in an acute-chronic ratio of less than 1.0 using the acute without food and 2.0 using the acute with food (Table 2). In the second laboratory in side-by-side tests, the acute value was 0.25 µg/l without food (Table 1) and 9.5 µg/l with food (Table 6). Because of the variation in hardness, and probably other water quality characteristics, and the results of acute and chronic tests in this laboratory, it seems inappropriate to calculate an acute-chronic ratio for Daphnia magna from these data.

Davies, et al. (1978) conducted an 18-month study to evaluate the effects of silver nitrate on survival and growth of rainbow trout (Table 2). The exposure was initiated with eyed embryos which hatched after 26 days. Premature hatching occurred in silver concentrations of 0.69, 0.34, and 0.17 µg/l. After a 2-month exposure, the length of fish exposed to these three high test concentrations was significantly ($p=0.05$) reduced. However, after three and one-half months of exposure only the length of the fish in the high concentration was significantly (p=0.05) less than the length of control fish. At the termination of the exposure, survival of fish exposed to 0.09 µg/l was similar to the 79.9 percent survival of control fish. Mortality of fish exposed to 0.17 and 0.34 µg/l was 17.2 and 36.6 percent greater, respectively, than mortality of control fish. The results of this chronic test and the comparable acute tests produced an acute-chronic ratio of 54 for silver and rainbow trout.

Davies and Goettl (1978) also investigated the effects of silver iodide on survival and growth of rainbow trout (Table 6). One toxicity test was initiated with eyed embryos and lasted for 13 months. These embryos hatched in eight days, and swim-up was completed in 17 days. Survival through swim-up was similar in all silver concentrations and ranged from 95.3 to 91.5 percent. Control mortality was not reported because of initial overcrowding of control tank. Mortality of post swim-up fry was 3.2 percent for the fish exposed to 0.03 µg/l and was above 18 percent for concentrations of 0.06 µg/l and higher. At the termination of the study the mean length of fish in all silver concentrations was not significantly (p=0.05) different from the mean length of control fish. Earlier growth measurements were not reported.

Another toxicity test with silver iodide was initiated with green embryos, and the exposure was for 10 months (Table 6). Hatching was completed after seven weeks and swim-up was completed in 12 weeks. At this time survival of embryos and sac fry at all test concentrations was similar to survival of control embryos and sac fry. However, survival after swim-up was only 73.2 percent in the high concentration of 0.40 µg/l. Survival of fish in silver concentrations of 0.18 µg/l and lower ranged from 96.4 to 98 percent and was similar to the control fish survival of 97.6 percent. Growth of control fish and fish exposed to silver was not significantly different (p=0.05) after 8 and 10 months. Earlier growth measurements were not reported. The difference between the results of the two chronic tests on silver iodide may have been due to embryonic acclimation to silver with the longer exposure of the green embryos (Davies and Giettl, 1978). The difference may also have been just experimental variation.

The chronic values from these three chronic toxicity studies with rainbow trout using a similar dilution water and measured concentrations ranged from 0.04 to 0.27 µg/l. Two of the three tests were started with eyed embryos, and both of these chronic values were lower than the chronic value from the test in which fertilized embryos were placed immediately into the exposure system. The length of exposure of the embryos to silver nitrate was intermediate between the length of exposure of embryos in the two silver iodide tests, and the chronic value in the silver nitrate test was intermediate between the two chronic values of the silver iodide tests.

Nebeker, et al. (Manuscript c), conducted an early life stage test for 90 days using rainbow (steelhead) trout. The chronic value of 12 µg/l was greater than the 96-hour LC_{50} value (Table 1) that Nebeker, et al. (1980) reported for flow-through tests using rainbow trout. In addition, this chronic value was two orders of magnitude greater than the chronic values reported by Davies, et al. (1978) and Davies and Goettl (1978) for rainbow trout. No acute-chronic ratio was calculated from the results of this early life stage test.

A chronic toxicity value of 18 µg/l for the saltwater mysid shrimp was determined (Table 2) in a flow-through, life-cycle test (Lussier and Gentile, 1980). In this experiment, groups of 20 juvenile shrimp were reared in each of five silver concentrations for 58 days at 20°C and 30 g/kg salinity. Responses examined included time of appearance of first brood, time of first spawn, mean brood size (larvae/female), growth of larvae, and survival of first filial generation. No spawning occurred at 103 µg/l, and time of spawning was delayed to seven days at 33.3 µg/l. Brood size was statistically ($p<0.05$) smaller at 33.3 µg/l as compared to controls. Larval survival was unimpaired and was at least 95 percent in all treatments, and larval growth was not retarded at any test concentration. The highest concentration of silver tested having no statistically significant effect on growth, reproduction, or survival was 10 µg/l. The 96-hour LC_{50} for this species in the same study was 250 µg/l, and the acute-chronic ratio for this species was 14.

Because of the variation in the results of chronic tests with rainbow trout and the problem with determining an acute-chronic ratio for Daphnia magna, neither a Final Acute-Chronic Ratio nor a Freshwater or Saltwater Final Chronic Value can be determined for silver.

Plant Effects

Data on the toxicity of silver to 13 freshwater plant species are listed in Table 4. The adverse effect concentrations range from 30 to 7,500 µg/l. Even though these tests were conducted in various growth media and different effects were measured, it appears that the adverse effects of silver on plants are unlikely at concentrations which will not adversely affect freshwater animals.

Fitzgerald (1967) studied the effect of halides on the toxicity of silver. He compared the algistatic activity of silver nitrate on Chlorella pyrenoidosa in the presence and absence of 12 mg/l of sodium chloride, sodium bromide, or sodium iodide. The results indicated that sodium chloride caused a slight but consistent decrease in the toxicity of silver nitrate. Sodium iodide caused the greatest decrease in toxicity of silver nitrate.

This decrease in toxicity was related to the solubility of the silver halide. The least soluble silver halide, silver iodide, was the least toxic. He also reported that both live and dead algae detoxified silver nitrate.

Stokes, et al. (1973) found that 30 µg/l of silver inhibited the growth of Chlorella vulgaris. In addition, two species of green algae isolated from small lakes which had high concentrations of heavy metals, especially copper and nickel, had higher tolerances to silver than algae of the same genus from the laboratory.

Information on the sensitivity of saltwater plants to silver is limited to the results of one test showing a 50 percent reduction in chlorophyll a production at 170 µg/l and a 50 percent decrease in cell number at 130 µg/l (Table 4). These EC_{50} values are intermediate to the range of acute values for saltwater animals.

Residues

Three insect species have been exposed to silver nitrate (Nehring, 1973) and bioconcentration factors that range from 15 to 240 were calculated from the data (Table 5). Bluegills were exposed during a 28-day test, and the bioconcentration factor was less than one (U.S. EPA, 1978).

No data are available concerning bioconcentration of silver by saltwater species.

Miscellaneous

Birge, et al. (1978) examined the toxicity of 11 trace metals. Silver was the most toxic to the embryos and larvae of both rainbow trout and largemouth bass, with the trout being more sensitive than the bass. Renewal exposure was maintained from fertilization through four days post-hatch. The marbled salamander was less sensitive than either fish species.

Soyer (1963) reported reduced development in sea urchin embryos at 0.5 µg/l after a 52-hours exposure (Table 6) and Calabrese, et al. (1973) found 100 percent mortality among American oyster larvae after a 2-day exposure to 10 µg/l. The lower concentration is much lower than the chronic value for the mysid shrimp. Also, summer glounder larvae are apparently more sensitive than embryos, but the reverse may be true for winter flounder (Tables 1 and 6).

Summary

Acute toxicity data for silver are available for 10 species of freshwater animals from nine different taxonomic families that perform a wide variety of community functions. The acute values range from 0.25 µg/l for *Daphnia magna* to 4,500 µg/l for the scud, *Gammarus pseudolimnaeus*. Fish are intermediate in sensitivity with acute values that range from 3.9 µg/l for the fathead minnow in soft water to 280 µg/l for rainbow trout in hard water.

The data base indicates that acute toxicity of silver apparently decreases as hardness increases. Silver chloride seems to be much less toxic than the very toxic silver nitrate. The relatively insoluble salts, silver thiosulfate and silver sulfide, were the least toxic. On the other hand silver iodide, when tested chronically at concentrations below its solubility limit, was as toxic as silver nitrate. Organic materials may also affect the toxicity of silver because the acute toxicity of silver nitrate to *Daphnia magna* when food was added to the water was much less than when food was not added to the water.

Four early life stage studies with the rainbow trout indicate that chronic toxicity may be influenced by the age of embryos with which the test was started and perhaps by the genetic variety of the rainbow trout.

Plants appear to be more resistant to silver than some animals, and thus their well-being is assured if the more sensitive animals are protected. The bioconcentration factors for silver range from less than one for bluegill to 240 for insect larvae.

Acute values for saltwater organisms ranged from 4.7 µg/l for the summer flounder to 1,400 µg/l for the sheepshead minnow. A life-cycle toxicity test conducted with the mysid shrimp showed that brood size was smaller at 33 µg/l as compared to controls. The highest concentration tested which had no statistically significant effect on reproduction and survival was 10 µg/l. One saltwater alga has been tested, and reduced cell numbers were recorded at 130 µg/l. No information is available showing the influence of environmental factors such as salinity, on toxicity of silver to saltwater organisms.

CRITERIA

For freshwater aquatic life the concentration (in µg/l) of total recoverable silver should not exceed the numerical value given by $e^{(1.72\,[\ln(\text{hardness})]-6.52)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$, the concentration of total recoverable silver should not exceed 1.2, 4.1, and 13 µg/l, respectively, at any time. The available data indicate that chronic toxicity to freshwater aquatic life may occur at concentrations as low as 0.12 µg/l.

For saltwater aquatic life the concentration of total recoverable silver should not exceed 2.3 µg/l at any time. No data are available concerning the chronic toxicity of silver to sensitive saltwater aquatic life.

Table 1. Acute values for silver

Species	Method*	Hardness (mg/l as CaCO$_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Rotifer, *Philodina acuticornis*	S, U	25	1,400	-	Bulkema, et al. 1974
Cladoceran, *Daphnia magna*	S, U	40	1.5	-	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	48	0.66	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	48	0.39	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	255	45	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	255	49	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	54	2.2	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	54	2.9	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	46	0.90	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	46	1.0	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	38	1.1	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	40	0.64	-	Lemke, Manuscript
Cladoceran, *Daphnia magna*	S, M	47	0.25	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	75	15	-	Lemke, Manuscript

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Cladoceran, *Daphnia magna*	S, M	75	8.4	-	Lemke, Manuscript
Scud, *Gammarus pseudolimnaeus*	FT, M	48	4,500	-	U.S. EPA, 1980a
Midge, *Tanytarsus dissimilis*	FT, M	48	3,200	-	U.S. EPA, 1980a
Rainbow trout, *Salmo gairdneri*	FT, M	31	5.3	-	Davies, et al. 1978
Rainbow trout, *Salmo gairdneri*	FT, M	20	6.2	-	Davies, et al. 1978
Rainbow trout, *Salmo gairdneri*	FT, M	26	8.1	-	Davies, et al. 1978
Rainbow trout, *Salmo gairdneri*	FT, M	350	13	-	Davies, et al. 1978
Rainbow trout, *Salmo gairdneri*	FT, M	-	29	-	Hale, 1977
Rainbow trout, *Salmo gairdneri*	FT, M	48	18	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	48	16	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	48	20	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	48	32	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	255	240	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	255	170	-	Lemke, Manuscript

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	S, M	255	240	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	255	280	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	54	14	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	54	12	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	54	48	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	54	54	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	46	6.9	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	46	8.4	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	46	12	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	46	110	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	29	7.6	-	Nebeker, et al. Manuscript b
Rainbow trout, *Salmo gairdneri*	FT, M	35	8.5	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	42	9.7	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	40	73	-	Lemke, Manuscript

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	S, M	37	84	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	26	11	-	Nebeker, et al. Manuscript b
Rainbow trout, *Salmo gairdneri*	FT, M	75	11.5	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	FT, M	75	10	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	75	25	-	Lemke, Manuscript
Rainbow trout, *Salmo gairdneri*	S, M	75	22.5	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	48	11	-	U.S. EPA, 1980a
Fathead minnow, *Pimephales promelas*	FT, M	33	3.9	-	Goettl & Davies, 1978
Fathead minnow, *Pimephales promelas*	FT, M	274	4.8	-	Goettl & Davies, 1978
Fathead minnow, *Pimephales promelas*	FT, M	48	11	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	48	12	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	48	30	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	48	23	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	255	150	-	Lemke, Manuscript

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	FT, M	255	110	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	255	230	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	255	270	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	54	11	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	54	14	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	54	20	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	46	5.3	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	46	3.9	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	46	6.7	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	46	12	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	38	5.8	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	40	5.6	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	36	7.4	-	Nebeker, et al. Manuscript b
Fathead minnow, *Pimephales promelas*	S, M	25	12	-	Lemke, Manuscript

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	S, M	39	9.7	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	75	6.3	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	75	5.0	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	75	10	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	S, M	75	8.7	-	Lemke, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	38	16	-	EG&G Bionomics, 1979
Speckled dace, *Rhinichthys osculus*	FT, M	30	4.9	-	Goettl & Davies, 1978
Speckled dace, *Rhinichthys osculus*	FT, M	250	14	-	Goettl & Davies, 1978
Flagfish, *Jordanella floridae*	FT, M	48	9.6	-	U.S. EPA, 1980a
Bluegill, *Lepomis macrochirus*	S, U	40	64	-	U.S. EPA, 1980a
Mottled sculpin, *Cottus bairdi*	FT, M	30	5.3	-	Goettl & Davies, 1978
Mottled sculpin, *Cottus bairdi*	FT, M	250	14	-	Goettl & Davies, 1978

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
		SALTWATER SPECIES			
Bay scallop (juvenile), Argopecten irradians	S, U	-	33	33	Nelson, et al. 1976
American oyster, Crassostrea virginica	S, U	-	5.8	-	Calabrese, et al. 1973
American oyster, Crassostrea virginica	S, U	-	24	-	MacInnes & Calabrese, 1978
American oyster, Crassostrea virginica	S, U	-	35	-	MacInnes & Calabrese, 1978
American oyster, Crassostrea virginica	S, U	-	32	20	MacInnes & Calabrese, 1978
Hardshell clam, Mercenaria mercenaria	S, U	-	21	21	Calabrese & Nelson, 1974
Copepod (adult), Acartia tonsa	S, M	-	36	36	U.S. EPA, 1980b
Mysid shrimp (juvenile), Mysidopsis bahia	FT, M	-	250	250	Lussier & Gentile, 1980
Atlantic silversides (juvenile), Menidia menidia	S, U	-	400	-	U.S. EPA, 1980b
Atlantic silversides (larva), Menidia menidia	S, U	-	110	210	U.S. EPA, 1980b
Summer flounder (larva), Paralichthys dentatus	S, U	-	4.7	4.7	U.S. EPA, 1980b
Sheepshead minnow (juvenile), Cyprinodon variegatus	S, M	-	1,400	1,400	U.S. EPA, 1980b

Table 1. (Continued)

Species	Method*	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value (µg/l)	Reference
Fourspine stickleback (adult), Apeltes quadracus	S, U	-	550	550	U.S. EPA, 1980b
Winter flounder (larva), Pseudopleuronectes americanus	S, U	-	500	500	U.S. EPA, 1980b

---

* S = static, FT = flow-through, U = unmeasured, M = measured

**All freshwater and saltwater acute toxicity data were derived with silver nitrate and all results are expressed as silver, not as the compound.

Freshwater:

Acute toxicity vs. hardness (see text)

Daphnia magna: slope = 2.35, intercept = -8.85, r = 0.89, P = 0.01, N = 14

Rainbow trout: slope = 1.30, intercept = -2.08, r = 0.75, P = 0.01, N = 30

Fathead minnow: slope = 1.50, intercept = -3.52, r = 0.83, P = 0.01, N = 28

Arithmetic mean acute slope = 1.72

Table 2. Chronic values for silver

Species	Test*	Chemical	Hardness (mg/l as $CaCO_3$)	Limits (µg/l)**	Chronic Value (µg/l)**	Reference
FRESHWATER SPECIES						
Cladoceran, *Daphnia magna*	LC	Silver nitrate	60	1.6-4.1	2.6	Nebeker, et al. Manuscript b
Cladoceran, *Daphnia magna*	LC	Silver nitrate	75	8.8-19.4	13	Nebeker, et al. Manuscript b
Cladoceran, *Daphnia magna*	LC	Silver nitrate	180	3.4-8.0	5.2	Nebeker, et al. Manuscript b
Cladoceran, *Daphnia magna*	LC	Silver nitrate	48	2.7-3.9	3.2	Nebeker, et al. Manuscript a
Cladoceran, *Daphnia magna*	LC	Silver nitrate	70	10.5-21.2	15	Nebeker, et al. Manuscript a
Cladoceran, *Daphnia magna*	LC	Silver nitrate	70	19.8-41.2	29	Nebeker, et al. Manuscript a
Rainbow trout, *Salmo gairdneri*	ELS	Silver nitrate	28	0.09-0.17	0.12	Davies, et al. 1978
Rainbow trout, (steelhead), *Salmo gairdneri*	ELS	Silver nitrate	37	8.9-15.9	12	Nebeker, et al. Manuscript c
SALTWATER SPECIES						
Mysid shrimp, *Mysidopsis bahia*	LC	Silver nitrate	-	10-33	18	Lussier & Gentile, 1980

---

* LC = life cycle or partial life cycle; ELS = early life stage

**Results are expressed as silver, not as the compound

Table 2. (Continued)

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
	Silver Nitrate		
Cladoceran, *Daphnia magna*	43*	22**	2.0
Rainbow trout, *Salmo gairdneri*	6.5***	0.12	54
Mysid shrimp, *Mysidopsis bahia*	250	18	14

---

* Result of acute test with food added to test solutions (Table 6).

** Arithmetic mean of 15 and 29 µg/l (Table 2).

***Arithmetic mean of 5.3, 6.2 and 8.1 µg/l (Table 1)

Table 3. Species mean acute intercepts, values, and acute-chronic ratios for silver

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
10	Scud, Gammarus pseudolimnaeus	5.77	-
9	Rotifer, Philodina acuticornis	5.52	-
8	Midge, Tanytarsus dissimilis	4.11	-
7	Bluegill, Lepomis macrochirus	0.112	-
6	Rainbow trout, Salmo gairdneri	0.0230	54
5	Mottled sculpin, Cottus bairdi	0.015	-
4	Speckled dace, Rhinichthys osculus	0.014	-
3	Flagfish, Jordanella florida	0.0123	-
2	Fathead minnow, Pimephales promelas	0.0121	-
1	Cladoceran, Daphnia magna	0.00192	2.0

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	SALTWATER SPECIES		
10	Sheepshead minnow, Cyprinodon variegatus	1,400	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
9	Fourspine stickleback, *Apeltes quadracus*	550	-
8	Winter flounder, *Pseudopleuronectes americanus*	500	-
7	Mysid shrimp, *Mysidopsis bahia*	250	14
6	Atlantic silversides, *Menidia menidia*	210	-
5	Copepod, *Acartia tonsa*	36	-
4	Bay scallop, *Argopecten irradians*	33	-
3	Hard shell clam, *Mercenaria mercenaria*	21	-
2	American oyster, *Crassostrea virginica*	20	-
1	Summer flounder, *Paralichthys dentatus*	4.7	-

---

* Ranked from least sensitive to most sensitive based on species mean acute intercept or species mean acute value.

Freshwater:

Final Acute Intercept = 0.00147 µg/l

Natural logarithm of 0.00147 = -6.52

Acute slope = 1.72 (see Table 1)

Final Acute Equation = $e^{(1.72[\ln(\text{hardness})]-6.52)}$

Saltwater Final Acute Value = 2.28 µg/l

Table 4. Plant values for silver

Species	Effect	Result* (µg/l)	Reference
	FRESHWATER SPECIES		
Alga (green), *Chlorella fusca*	Complete inhibition of growth	100**	Stokes, et al. 1973
Alga (green), *Chlorella fusca*	Inhibition of growth	50**	Stokes, et al. 1973
Alga (green), *Chlorella pyrenoidosa*	Inhibition of growth	100	Fitzgerald, 1967
Alga (green), *Chlorella pyrenoidosa*	Lethal	1,000	Fitzgerald, 1967
Alga (green), *Chlorella variegata*	Toxic	420	Palmer & Maloney, 1955
Alga (green), *Chlorella vulgaris*	Inhibition of growth	50**	Hutchinson & Stokes, 1975
Alga (green), *Chlorella vulgaris*	Inhibiton of growth	30**	Stokes, et al. 1973
Alga (green), *Scenedesmus acuminatus*	Complete inhibition of growth	100**	Stokes, et al. 1973
Alga (green), *Scenedesmus acutiformis*	Complete inhibition of growth	200**	Stokes, et al. 1973
Alga (green), *Scenedesmus obliquus*	Toxic	420	Palmer & Maloney, 1955
Alga (green), *Scenedesmus obliquus*	Threshold toxicity	50	Bringman & Kuhn, 1959
Alga (diatom), *Gomphonema parvulum*	Toxic	420	Palmer & Maloney, 1955
Alga (diatom), *Nitzschia palea*	Toxic	420	Palmer & Maloney, 1955

Table 4. (Continued)

Species	Effect	Result* (µg/l)	Reference
Alga (blue-green), Cylindrospermum licheniforme	Toxic	420	Palmer & Maloney, 1955
Alga (blue-green), Microcystis aeruginosa	Toxic	420	Palmer & Maloney, 1955
Waterweed, Elodea canadensis	Inhibition of oxygen evolution	100	Brown & Rattigan, 1979
Waterweed, Elodea canadensis	Phytotoxicity	7,500	Brown & Rattigan, 1979
Duckweed, Lemna minor	Phytotoxicity	270	Brown & Rattigan, 1979
	SALTWATER SPECIES		
Alga, Skeletonema costatum	96-hr EC50, chlorophyll a	170	U.S. EPA, 1978
Alga, Skeletonema costatum	96-hr EC50, cell numbers	130	U.S. EPA, 1978

---

* All freshwater and saltwater plant values were derived with silver nitrate except where indicated and all results are expressed as silver, not as the compound.

**Authors did not specify silver compound.

Table 5. Residues* for silver

Species	Tissue	Hardness (mg/l as $CaCO_3$)	Bioconcentration factor	Duration (days)	Reference
			FRESHWATER SPECIES		
Mayfly, *Ephemerella grandis*	Whole body	62	35**	7	Nehring, 1973
Mayfly, *Ephemerella grandis*	Whole body	65	240**	10	Nehring, 1973
Stonefly, *Claasenia sabulosa*	Whole body	34	15**	3	Nehring, 1973
Stonefly, *Pteronarcys californica*	Whole body	32	21**	6	Nehring, 1973
Stonefly, *Pteronarcys californica*	Whole body	31	170**	7	Nehring, 1973
Stonefly, *Pteronarcys californica*	Whole body	30	79**	15	Nehring, 1973
Bluegill, *Lepomis macrochirus*	Whole body	-	<1	28	U.S. EPA, 1978

---

* All results were derived with silver nitrate.

**Bioconcentration factors have been converted from dry weight to wet weight.

Table 6. Other data for silver

Species	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
			FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	274	24 hrs	LC50	3.4	Bringmann & Kuhn, 1977
Cladoceran, *Daphnia magna*	47	48 hrs	LC50**	9.5	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	70	48 hrs	LC50**	43	Lemke, Manuscript
Mayfly, *Ephemerella grandis*	31	7 days	LC50	<4	Nehring, 1973
Mayfly, *Ephemerella grandis*	30	15 days	LC50	8.8	Nehring, 1973
Stonefly, *Pteronarcys californica*	65	10 days	LC50	<9	Nehring, 1973
Rainbow trout, *Salmo gairdneri*	93-105	28 days	LC50	10	Birge, et al. 1978
Rainbow trout (eyed embryos), *Salmo gairdneri*	28	13 mos	Chronic limits***	0.03-0.06	Davies & Goettl, 1978
Rainbow trout (green embryos), *Salmo gairdneri*	29	10 mos	Chronic limits***	0.18-0.40	Davies & Goettl, 1978
Fathead minnow, *Pimephales promelas*	38	96 hrs	100% mortality (silver thiosulfate)	280,000	EG&G Bionomics, 1979
Fathead minnow, *Pimephales promelas*	38	96 hrs	No mortality (silver sulfide gel)	240,000	EG&G Bionomics, 1979
Fathead minnow, *Pimephales promelas*	38	96 hrs	No mortality (silver sulfide)	13,000	EG&G Bionomics, 1979

Table 6. (Continued)

Species	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Fathead minnow, *Pimephales promelas*	38	96 hrs	LC50 (2,000 mg Cl^-/l)	5,600	EG&G Bionomics, 1979
Fathead minnow, *Pimephales promelas*	38	96 hrs	LC50 (1,000 mg Cl^-/l)	510	EG&G Bionomics, 1979
Fathead minnow, *Pimephales promelas*	38	96 hrs	LC50 (500 mg Cl^-/l)	2,100	EG&G Bionomics, 1979
Fathead minnow, *Pimephales promelas*	131	96 hrs	LC50 (silver thiosulfate)	>250,000	Terhaar, et al. 1972
Bluegill, *Lepomis macrochirus*	180	6 mos	Tolerated	70	Coleman & Cearley, 1974
Largemouth bass, *Micropterus salmoides*	93-105	8 days	LC50	110	Birge, et al. 1978
Largemouth bass, *Micropterus salmoides*	180	24 hrs	Lethal	70	Coleman & Cearley, 1974
Marbled salamander, *Ambystoma opacum*	93-105	8 days	LC50	240	Birge, et al. 1978
		SALTWATER SPECIES			
Red alga (sporling), *Plumaria elegans*	-	18 hrs	98% mortality	1,000	Boney, et al. 1959
Bay scallop (juvenile), *Argopecten irradians*	-	4 days	15% increased O_2 uptake	22	Nelson, et al. 1976
American oyster (larva), *Crassostrea virginica*	-	2 days	100% mortality	10	Calabrese, et al. 1973
American oyster (larva), *Crassostrea virginica*	-	12 days	50% mortality	25	Calabrese, et al. 1977
American oyster, *Crassostrea virginica*	-	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974

Table 6. (Continued)

Species	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Hard-shell clam, Mercenaria mercenaria	-	2 days	100% mortality	45	Calabrese & Nelson, 1974
Hard-shell clam, Mercenaria mercenaria	-	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Hard-shell clam (larva), Mercenaria mercenaria	-	10 days	LC50	32	Calabrese, et al. 1977
Soft-shell clam, Mya arenaria	-	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Blue mussel, Mytilus edulis	-	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Mud snail, Nassarius obsoletus	-	3 days	Depression of oxygen consumption	500	MacInnes & Thurberg, 1973
Mud snail, Nassarius obsoletus	-	3 days	Distressed behavior, snail unable to move	250	MacInnes & Thurberg, 1973
Surf clam (larva), Spisula solidissima	-	15 days	Significant increase in oxygen consumption	50	Thurberg, et al. 1975
Surf clam (juvenile), Spisula solidissima	-	4 days	Significant increase in oxygen consumption	10	Thurberg, et al. 1975
Surf clam (adult), Spisula solidissima	-	4 days	Significant increase in oxygen consumption	50	Thurberg, et al. 1975
Common barnacle (adult), Balanus balanoides	-	2 days	90% mortality	400	Clarke, 1947
Common barnacle (adult), Balanus balanoides	-	5 days	90% mortality	200	Clarke, 1947

Table 6. (Continued)

Species	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Sea urchin, *Arbacia lixula*	-	52 hrs	Reduced embryo development significantly	0.5	Soyer, 1963
Mummichog (adult), *Fundulus heteroclitus*	-	4 days	*In vivo* inhibition of 3 liver enzymes	30	Jackim, et al. 1970
Mummichog (adult), *Fundulus heteroclitus*	-	2 days	Degeneration of lateral line and olfactory sensory structure	500	Gardner, 1975
Cunner, *Tautogolabrus adspersus*	-	4 days	Significant depression of oxygen consumption	120	Thurberg & Collier, 1977
Cunner, *Tautogolabrus adspersus*	-	4 days	Decreased oxygen consumption depressed activity of a liver enzyme	500	Gould & MacInnes, 1977
Summer flounder (embryo), *Paralichthys dentatus*	-	96 hrs	LC50	140	U.S. EPA, 1980b
Summer flounder (embryo), *Paralichthys dentatus*	-	96 hrs	LC50	8.0	U.S. EPA, 1980b
Summer flounder (embryo), *Paralichthys dentatus*	-	96 hrs	LC50	16	U.S. EPA, 1980b
Summer flounder (embryo), *Paralichthys dentatus*	-	96 hrs	LC50	48	U.S. EPA, 1980b
Winter flounder (embryo), *Pseudopleuronectes americanus*	-	96 hrs	LC50	450	U.S. EPA, 1980b

Table 6. (Continued)

Species	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Winter flounder (embryo), Pseudopleuronectes americanus	-	96 hrs	LC50	300	U.S. EPA, 1980b
Winter flounder (embryo), Pseudopleuronectes americanus	-	96 hrs	LC50	270	U.S. EPA, 1980b
Winter flounder (embryo), Pseudopleuronectes americanus	-	96 hrs	LC50	200	U.S. EPA, 1980b

---

* All freshwater and saltwater data were derived with silver nitrate except where indicated and all results are expressed as silver, not as the compound.

** Animals were fed during test.

***Tests on silver iodide.

REFERENCES

Birge, W.J., et al. 1978. Embryo-larval Bioassays on Inorganic Coal Elements and _in situ_ Biomonitoring of Coal-waste Effluents. _In_: D.E. Samuel, et al. (eds.), Surface Mining and Fish/Wildlife Needs in the Eastern United States. U.S. Dept. Int. Fish Wildl. Serv., FWS/OBS-78/81, Dec. 1978. p. 97.

Boney, A.D., et al. 1959. The effects of various poisons on the growth and viability of sporelings of the red alga _Plumaria elegans_ (Bonnem.) Schm. Biochem. Pharmacol. 2: 37.

Bringmann, G. and R. Kuhn. 1959. Comparative water-toxicology investigations on bacteria, algae, and daphnids. Ges. Ind. 80: 115.

Bringmann, V.G. and R. Kuhn. 1977. Report on the damaging action of water pollutants on _Daphnia magna_. Wass. Abwass-Forsch. 10. 5: 161.

Brown, B.T. and B.M. Rattigan. 1979. Toxicity of soluble copper and other metal ions to _Elodea canadensis_. Environ. Pollut. 20: 303.

Buikema, A.L., Jr., et al. 1974. Evaluation of _Philodina acuticornis_ (Rotifera) as a bioassay organism for heavy metals. Water Res. Bull. 10: 648.

Calabrese, A. and D.A. Nelson. 1974. Inhibition of embryonic development of the hard clam *Mercenaria mercenaria* by heavy metals. Bull. Environ. Contam. Toxicol. 11: 92.

Calabrese, A., et al. 1973. The toxicity of heavy metals to the embryos of the American oyster (*Crassostrea virginica*). Mar. Biol. 18: 162.

Calabrese, A., et al. 1977. Effects of cadmium, mercury and silver on marine animals. Mar. Fish. Rev. 39: 5.

Chambers, C.W. and C.M. Proctor. 1960. The bacteriological and chemical behavior of silver in low concentrations. U.S. Dept. Health, Edu. and Welfare. PHS Tech. Rep. W60-4. p. 1.

Chapman, G.A., et al. Effects of water hardness on the toxicity of metals to *Daphnia magna*. Status Report. U.S. Environ. Prot. Agency, Corvallis, Oregon. (Manuscript)

Clarke, G.L. 1947. Poisoning and recovery in barnacles and mussels. Biol. Bull. 92: 73.

Coleman, R.L. and J. Cearley. 1974. Silver toxicity and accumulation in largemouth bass and bluegill. Bull. Environ. Contam. Toxicol. 12: 53.

Davies, P.H. and J.P. Goettl, Jr. 1978. Evaluation of the Potential Impacts of Silver and/or Silver Iodide on Rainbow Trout in Laboratory and High Mountain Lake Environments. In: D.A. Klein (ed.), Environmental Impacts of Artificial Ice Nucleating Agents. Dowden, Hutchinson and Ross, Inc., Stroudsburg, Pennsylvania. p. 149.

Davies, P.H., et al. 1978. Toxicity of silver to rainbow trout (*Salmo gairdneri*). Water Res. 12: 113.

Dyck, W. 1968. Adsorption and coprecipitation of silver on hydrous ferric oxides. Can. Jour. Chem. 46: 1441.

EG&G Bionomics. 1979. The acute toxicity of various silver compounds to the fathead minnow (*Pimephales promelas*). Natl. Assoc. Photo. Manu., Inc., Harrison, New York. p. 1, Tables 1-30, Appendix I-IV.

Fitzgerald, G.P. 1967. The algistatic properties of silver. Water Sew. Works. 114: 185.

Gardner, G.R. 1975. Chemically Induced Lesions in Estuarine or Marine Teleosts. In: W.E. Ribeline and G. Migaki (eds.), The Pathology of Fishes. Univ. Wisconsin Press, Madison, Wisconsin. p. 657.

Goettl, J.P., Jr. and P.H. Davies. 1978. Water pollution studies. Job 6. Study of the effects of metallic ions on fish and aquatic organisms. Job Progress Rep. Fed. Aid Proj. F-33-R-13. Colorado Div. Wildl. p. 6.

Gould, E. and J.R. MacInnes. 1977. Short-term effects of two silver salts on tissue respiration and enzyme activity in the cunner (Tautogalabrus adspersus). Bull. Environ. Contam. Toxicol. 18: 401.

Hale, J.G. 1977. Toxicity of metal mining wastes. Bull. Environ. Contam. Toxicol. 17: 66.

Hem, J.D. 1970. Study and interpretation of the chemical characteristics of natural waters. U.S. Geol. Surv. Water-Supply Pap. 1473. Washington, D.C. p. 202.

Hutchinson, T.C. and P.M. Stokes. 1975. Heavy metal toxicity and algal bioassays. Water Quality Parameters. ASTM SPT 573: 320.

Jackim, E., et al. 1970. Effects of metal poisoning on five liver enzymes in the killifish (Fundulus heteroclitus). Jour. Fish. Res. Board Can. 27: 383.

Kharkar, D.P., et al. 1968. Stream supply of dissolved silver, molybdenum, antimony, selenium, chromium, cobalt, rubidium, and cesium to the oceans. Geochim. Cosmochim. Acta. 32: 285.

Lemke, A.E. Comprehensive report - Interlaboratory comparison: acute testing set. (Manuscript).

Lussier, S.L. and J.H. Gentile. Chronic toxicity of copper and silver to the mysid shrimp *Mysidopsis bahia*. U.S. Environ. Prot Agency, Environ. Res. Lab., Narragansett, Rhode Island. (Manuscript)

MacInnes, J.R. and A. Calabrese. 1978. Responses of Embryos of the American Oyster *Crassostrea virginica* to Heavy Metals at Different Temperatures. *In*: D.S. Mclusky and A.J. Berry (eds.), Physiology and Behavior of Marine Organisms. Proc. 12th European Symp. on Marine Biol. p. 195.

MacInnes, J.R. and F.P. Thurberg. 1973. Effects of metals on the behavior and oxygen consumption of the mud snail. Mar. Pollut. Bull. 4: 185.

Nebeker, A.V., et al. Toxicity of silver and endosulfan to rainbow trout, fathead minnow, and *Daphnia magna*. (Manuscript a)

Nebeker, A.V., et al. *Daphnia magna* static renewal life cycle tests. Final report of round-robin testing. U.S. Environ. Prot. Agency. (Manuscript b)

Nebeker, A.V., et al. Sensitivity of steelhead early life stages (embryolarval) to silver nitrate. (Manuscript c)

Nehring, R.B. 1973. Heavy metal toxicity in two species of aquatic insects. Masters Thesis. Colorado State Univ., Fort Collins, Colorado.

Nehring, R.B. 1976. Aquatic insects as biological monitors of heavy metal pollution. Bull. Environ. Contam. Toxicol. 15: 147.

Nelson, D.A., et al. 1976. Biological effects of heavy metals on juvenile bay scallops, Argopecten irradians, in short-term exposures. Bull. Environ. Contam. Toxicol. 16: 275.

Palmer, C.M. and T.E. Maloney. 1955. Preliminary screening for potential algicides. Ohio Jour. Sci. 55: 1.

Soyer, J. 1963. Contribution a l'etude des effects biologiques du mercure et de l'argent dans l'eau de mer. Vie et Milieu. 14: 1.

Stokes, P.M., et al. 1973. Heavy metal tolerance in algae isolated from polluted lakes near the Sudbury, Ontario smelters. Water Pollut. Res. Can. 8: 178.

Terhaar, G.J., et al. 1972. Toxicity of photographic processing chemicals to fish. Photographic Sci. Engr. 16: 370.

Thurberg, F.P. and R.S. Collier. 1977. Respiratory response of cunners to silver. Mar. Pollut. Bull. 8: 40.

Thurberg, F.P., et al. 1974. Effects of Silver on Oxygen Consumption of Bivalves at Various Salinities. In: F.J. Vernberg and W.B. Vernberg (eds.), Pollution and Physiology of Marine Organisms. Academic Press, New York. p. 67.

Thurberg, F.P., et al. 1975. Respiratory Response of Larval, Juvenile, and Adult Surf Clams, Spisula solidissima, to Silver. In: J.J. Cech, Jr., et al. (eds.), Respiration of Marine Organisms. Trigom. Pub., South Portland, Maine. p. 41.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. EPA Contract No. 68-01-4646. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1980a. Unpublished laboratory data. Environ. Res. Lab., Duluth, Minnesota.

U.S. EPA. 1980b. Unpublished laboratory data. Environ. Res. Lab., Narragansett, Rhode Island.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Silver is a frequent contaminant of normal human tissues, generally at $\leq$ 1 mg/kg in the ash (Tipton and Cook, 1963). For an extensive tabulation of silver concentrations in the tissues of normal individuals, disease victims, and people with argyria, see Smith and Carson (1977). Anspaugh, et al. (1971) of Lawrence Livermore Laboratory have also compiled data from the published literature on the silver content of human tissues. Most reported values have been based on ash weight or dry weight and are rather difficult to compare since analytical procedures at such low concentrations vary in their accuracies. Data in Table 1, adapted from Hamilton, et al. (1972/1973), however, seems to be in agreement with most reports.

Silver concentrations in human tissues apparently increase with age. It has been detected, however, in human placentae (Mischel, 1956) and fetal livers (Robkin, et al. 1973). Absorption upon exposure or the extent of exposure, itself, may vary considerably among normals as reflected in tissue levels. For example, the silver content of the hair of school children from 21 school districts in Silesia, Poland, ranged from 0.23 to 1.96 mg/kg (average 0.69 mg/kg; analysis by neutron activation) (Dutkiewicz, et al. 1978).

Ingestion from Water

Natural fresh waters contain an average of 0.2 μg/l silver, and seawater contains 0.24 μg/l (Boyle, 1968). Water-analysis data from many literature sources have been combined in Table 2.

TABLE 1

Silver Content in Healthy Human Tissues in the United Kingdom*

	No.	Ag, ug/g Wet Wt.
Blood (U.K. Master Mix)		0.01 ± 0.005
Blood (U.K.)	93	0.008 ± 0.0008
Whole brain	10	0.004 ± 0.002
Frontal lobe	2	0.003 + 0.001
Basal ganglia	2	0.004 ± 0.002
Whole kidney	8	0.002 + 0.0002
Cortex	8	0.001 ± 0.0002
Medulla	8	0.002 ± 0.0002
Liver	11	0.006 ± 0.002
Lung	11	0.002 + 0.0001
Lymph nodes	6	0.001 ± 0.0002
Muscle	6	0.002 + 0.0005
Testis	5	0.002 + 0.0004
Ovary	6	0.002 + 0.0005
Bone (rib) from patient who lived in:		
Hard water area	22	1.1 ± 0.2 (ash)
Soft water area	22	1.1 ± 0.2 (ash)

*Source: Hamilton, et al. 1972/1973

TABLE 2

Silver in Natural U.S. Waters

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Rainfall	–	–	0.002–0.216	St. Louis, Missouri		Rattonetti, 1974
Precipitation	0	0	0.02			
Precipitation (AgI seeded)	–	–	0.001–4.5	–	Typically 0.01–0.3 ppb Ag	Cooper & Jolly, 1969
Snowfall (AgI seeded)	–	–	0.11 (0.13 neutron activation anal.)	–		Warburton, 1969
Freshwater	–	–	0.01–0.7 0.13	– –		Hawkes & Webb, 1962 Bowen, 1966
Springs and surface freshwaters	–	–	0.2	All	Widely diffused, marked regional variations. Surface waters usually have less Ag than springs	Boyle, 1968
Hot springs: SO$_2$, NaCl, HCO$_3$–, borate, sulfate carbonate	5.3–9.1	0	up to 43,000 in siliceous	Steamboat Springs, Nevada		Boyle, 1968
Steam well: NaCl, CaCl$_2$, KCl	–	–	100–300 in water up to 13,000,000 in residue	Niland, California		Boyle, 1968
Spring and well waters	–	36%	10	Near Salton Sea, California	Geothermal brines have higher concn. of Ag and other trace metals than municipal or industrial wastewaters. Two of these samples had Ag content in excess of drinking water standards.	Bradford, 1971
Desert well brines	–	50%	10			
Oil well brines	–	–	0.1	California		Boyle, 1968
Vadose mine waters: SiO$_2$, Mg, Fe, Al, Ca, Cu, Mn, SO$_4$	Acid	–	207	Comstock Lode, Nevada		Boyle, 1968
Deep mine waters: sulfate, carbonate	Alkaline to neutral	–	3.3	Comstock Lode, Nevada	Temperature, 116–170°F	Boyle, 1968

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Seawater	–	–	0.15–2.9 (0.29) average	All	Run-off is of minor importance. Like Ba, Ag concentrates with increasing depth and in areas of high organic productivity. May be less concentrated near shores.	
Seawater	–	–	0.3	–		Lanford, 1969
Seawater	–	–	0.16	Gulf of Mexico		Bowen, 1966
Seawater	–	–	0.145	40 miles west of San Francisco		Boyle, 1968
Seawater	–	–	0.15–0.3	–		Boyle, 1968
Lakes	–	–	0.1–3.5	Maine		Boyle, 1968
Lakes	–	86%	0.1 (average) 6.0 (maximum)	California	Samples collected from 170 High Sierra Lakes.	Bradford, et al. 1968
Lake, ground, and Ottawa River water	–	–	0.006–0.7	Near Chalk River Nuclear Laboratory		Merritt, 1971
Agricultural drainage	–	100%	0.8 (1.0 maximum)	Coachella Valley, California		Bradford, 1971
Lakes	–	33%	10	Near Sudbury, Ontario	After 60 years of copper smelting	Stokes, et al. 1973
Lakes, streams, and rivers	–		10–200 (in residues)	U.S.		Boyle, 1968

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Surface waters	–	22.4%	0.10–3.0 (0.3 average)	California		Myers, et al. 1958
Stream water	–	–	0.00006–0.0062	St. Louis, Missouri		Klein, 1972
Rivers	–	–	up to 1.0	N. America & Norway		Boyle, 1968
Large rivers	–	–	0–0.94	North America		Boyle, 1968
U.S. river basins	–	6.6%	2.6 (38 maximum)	U.S.		Kopp & Kroner, 1970
					Detection limits for Kopp & Kroner were ppb.	Page, 1974
Northeast						
River Basin	–	14.3%	1.9 (6.0 maximum)	Northeastern U.S.	Includes New Jersey	Kopp & Kroner, 1970
St. Lawrence River	–	29.6%	2.6 (6.0 maximum)	Massena, New York		Kopp & Kroner, 1970
Hudson River	–	–	0.13–0.59	Green Island, New York		Durum & Haffty, 1961
North Atlantic						
River Basin	–	5.3%	0.9 (2.5 maximum)	U.S.		Kopp & Kroner, 1970
Delaware River	–	11.1%	1.1 (8.2 maximum)	Trenton, NJ		Kopp & Kroner, 1970
Delaware River	–	7.03%	3	–		Kopp & Kroner, 1967
Susquehanna River	–	–	0–0.29	Conowingo, MD		Durum & Haffty, 1961
Susquehanna River	–	–	0.39	–		Andelman, 1973
Southeast						
River Basin	–	5.5%	0.4 (0.7 maximum)	U.S.		Kopp & Kroner, 1970
Apalachicola River	–	–	0.058–0.11	Near Bloustown, Florida		Durum & Haffty, 1961
Mobile River	–	–	0.085–0.28	Mt. Vernon Landing, Alabama		
Neuse River	–	–	0.52	North Carolina	Groundwater lithology: Slate	Andelman, 1973
Neuse River	–	–	0.56	North Carolina	Shale	Andelman, 1973
Neuse River	–	–	0.25	North Carolina	Granite	Andelman, 1973
Neuse River	–	–	0.86	North Carolina	Shale and schist	Andelman, 1973
Neuse River	–	–	0.30	North Carolina	Cretaceous sand	Andelman, 1973
Neuse River	–	–	–	North Carolina	Tertiary lime	Andelman, 1973
Neuse River	–	–	0.37 (average)	North Carolina	Standard deviation = 49 based on samples taken at 25 locations.	Andelman, 1973

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Tennessee River Basin	–	0%	–	Tennessee and adjacent areas		Kopp & Kroner, 1970
Ohio River Basin	–	5.4%	2.1 (8.2 maximum)	U.S.		Kopp & Kroner, 1970
Youghiogheny River	–	–	0.05–1.0	West Newton, Pennsylvania	These primary streams receive acid mine drainage, but Ag was not detected 50 miles downstream in Toronto, Ohio	Kopp & Kroner, 1967
Kiskimintas River	–	–	0.5–1.3	Apollo, Pennsylvania		
Allegheny River	–	5.0%	2.0	Pittsburgh, Pennsylvania		Kopp & Kroner, 1970
Monongahela River	–	8.3%	2.0 (4.7 maximum)	Pittsburgh, Pennsylvania		Kopp & Kroner, 1970
Monongahela River	–	5.0%	4.0	Pittsburgh, Pennsylvania		Kopp & Kroner, 1967
Kanawha River	–	12.9%	1.2 (3.0 maximum)	Winfield Dam, West Virginia		Kopp & Kroner, 1970
Ohio River		60%	0.6–1			Kroner & Kopp, 1965
Great Lakes		14 1				Kroner & Kopp, 1965
Lake Erie Basin	–	6.4%	5.3 (9.0 maximum)	U.S.		Kopp & Kroner, 1970
Cuyahoga River	–	0	ND	Cleveland, Ohio	Receives effluents from automotive, meat-packaging and paper industries	Kopp & Kroner, 1967
Maumee River	–	12.5%	5.3 (9.0 maximum)	Toledo, Ohio	Travels from Ft. Wayne, Indiana through industrial complexes and receives agricultural, petrochemical and metal working wastes.	Kopp & Kroner, 1970
Maumee River	–	12.5%	3.6 (6.0 maximum)	Toledo, Ohio		
Upper Mississippi River Basin	–	5.4	3.4 (6.0 maximum)	U.S.		Kopp & Kroner, 1970
Western Great Lakes Basin	–	9.1%	1.4	U.S.		Kopp & Kroner, 1970
Detroit River	–	–	1.0 (3.8 maximum)	Detroit, Michigan		Kopp & Kroner, 1970
Missouri River Basin	–	4.1%	1.2 (1.5 maximum)	U.S.		Kopp & Kroner, 1970

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Southwest-Lower Mississippi Basin	–	4.5%	4.3 (9.0 maximum)	U.S.		Kopp & Kroner, 1970
Mississippi River	–	–	0. 0.22	Baton Rouge, Louisiana		Durum & Haffty, 1961
Mississippi River	–	–	0.26	–		Andelman, 1973
Mississippi River		12				Kroner & Kopp, 1965
Missouri River		57	0.2–20			Kroner & Kopp, 1965
Atchafalaya River	–	–	ND–0.33	Krotz Springs, Louisiana		Durum & Haffty, 1961
Colorado River Basin	–	18%	5.8 (38 maximum)	U.S.		Kopp & Kroner, 1970
Animas River	–	45%	2.9 (7.0 maximum)	Cedar Hill, New Mexico		Kopp & Kroner, 1970
Colorado River	–	13.6%	16 (38 maximum)	Loma, Colorado		Kopp & Kroner, 1970
Colorado River		0	ND			Kopp & Kroner, 1965
Colorado River	–	–	0–1.0	Yuma, Arizona		Durum & Haffty, 1961
Western Gulf Basin	–	4.3%	3.5 (6.6 maximum)	U.S.		Kopp & Kroner, 1970
Pacific Northwest Basin	–	8.6%	0.9 (3.7 maximum)	U.S.		Kopp & Kroner, 1970
Columbia River	–	–	0.09–0.15	Near The Dalles, Oregon		Durum & Haffty, 1961
Columbia River		0	0			Kopp & Kroner, 1970
Clearwater River	–	–	0.1	Lewiston, Idaho	1 occurrence	Kopp & Kroner, 1970
Pend Oreille River	–	–	0.2	Albeni Falls Dam, Idaho	1 occurrence	Kopp & Kroner, 1970
Snake River	–	–	0.5–1.3	Payette, Idaho	2 occurrences	Kopp & Kroner. 1970
Snake River	–	–	1.4	Wawawai, Washington	1 occurrence	Kopp & Kroner, 1970
California Basin	–	0	ND	California		Kopp & Kroner, 1970
Sacramento River	–	–	0–0.16	Sacramento, California		Durum & Haffty, 1961
San Fernando Valley	–	–	20	California	Estimated in wastewater	Bargman & Garber, 1973
Great Basin	–	5.3%	0.3	Nevada	1 occurrence	Kopp, 1969
Alaska	–	5.6%	1.1	Alaska		Kopp, 1969
Yukon River	–	–	0.20–0.31	Mountain Village, Alaska		Durum & Haffty, 1961

Kopp and Kroner (1970) found silver in 6.6 percent of 1,577 surface water samples collected in the United States. Concentrations in samples containing silver varied from 0.1 to 38 µg/l with a mean of 2.6 µg/l. The highest silver concentration was in the Colorada River at Loma, Colorado. Upstream industries included an old gold-copper-silver mine; an oil shale extraction plant at Rifle; uranium plants at Rifle, Grand Junction, and Gunnison; and a gasoline and coke refinery 1 mile from Loma.

Another striking example of elevated silver concentrations was found in 280 miles of streams and lakes in the Lower North Canadian River (LNCR) Basin of Oklahoma. The range of silver concentrations varied from undetectable to 25 µg/l in samples collected during all seasons. Water and sediment samples were collected at eight mainstream stations, eight tributary stream stations, and four Lake Eufaula stations. The LNCR also contained extraordinarily high concentrations of other trace elements and nutrients. The probable reason for the unusually high silver concentrations was the low water volume in some of the sampling streams. For example, the maximum concentration of silver was detected on the Soldier Creek Tributary (pH 7) which drained wastes from the northeast corner of Tinker Air Force Base. Silver was never detected at the sampling station closest to the Henryetta zinc smelter, but even the zinc concentration was lowest there (Frank, 1969).

Photoprocessing effluents usually contain $Ag(S_2O_3)_2^{-3}$, dissociation constant 3.5×10^{-14}, AgBr solubility product 4.8×10^{-13}

at 25°C or Ag_2S. Thus, under normal circumstances, they contain no free silver ions. Municipal biological treatment plants receiving photoprocessing wastes have not suffered any loss in efficiency from them. Some photoprocessing plants have even installed biological treatment plants themselves with up to 5 mg Ag/l in the water and 250 mg Ag/l in the aeration tank sludge. Since silver was present predominantly as Ag_2S with small amounts of metallic silver, the biological system was not adversely affected. Eastman Kodak activated sludge plant effluent contained 1 mg Ag/l; no soluble silver was detected (i.e., $<$ 20 µg/l or $<$ 20 ppb).

The Genesee River in New York has received photoprocessing effluents for approximately 70 years. In 1973, on most sampling dates from May 31 to October 17, it contained 20 µg/l silver. However, levels of 90 to 260 µg/l were detected in June. Sediments contained up to 150 mg/kg silver dry weight. Raw Lake Ontario water at the Eastman Kodak intake pipe contained 1 µg/l silver (Bard, et al. 1976).

At 0.04 g Ag/l and 0.01 g H_2S+HS^- per liter, AgSH is the major silver species normally present in freshwater, being present in concentrations up to 10-fold greater than the concentration of Ag^+ and AgCl. In seawater, there is more $AgCl_2^-$ than AgSH, and Ag^+ concentrations are trivial. Other species of minor or negligible importance in seawater are AgBr, $Ag(SH)_2^-$, AgF, AgOH, AgI, $AgNO_3$, $Ag(NO_2)_2^-$, and $AgSO_4$. The waters are oversaturated with silver by 7 to 12 times what is expected from available thermodynamic data (Jenne, et al. 1977).

The silver content of natural precipitates (i.e., stream sediments, etc.) has been discussed by Boyle (1968). The silver content of U.S. natural precipitates ranges from nil to 1,160 mg/kg. Turekian found 0.4 to 15.0 mg/kg silver in the suspended matter of 18 U.S. rivers. The Susquehanna River in Pennsylvania, which contained the highest concentration of silver, was estimated to be transporting 4.5 tons* of silver per year to the ocean (Turekian and Scott, 1967).

In the Lower North Canadian River (LNCR), the range of silver content in the ash of total suspended solids (silt plus microorganisms) was from undetected to 0.008 mg/kg, except at the station where the highest silver concentration was found in the water. Here, the silver content ranged from 15 to 50 mg/kg in the ash (Frank, 1969).

Silver concentrations of 0.05 to 45 µg/l have been found in effluents from municipal waste treatment plants. Silver concentrations as high as 900 mg/kg in sewage sludge have been reported (Smith and Carson, 1977).

Bruland, et al. (1974) studied the extent of metal pollution in the Southern California Coastal Zone which received Los Angeles area sewage. The average flux of anthropogenic silver into the sediments of the California Coastal Basin was estimated to be 50 percent greater than the average flux of natural silver (0.09

*A mathematical error in the calculations lead to the report itself stating 45 tons.

versus 0.06 $\mu g/cm^2/year$). The flux of anthropogenic silver to the sediments was calculated to be 11 MT/year/12,000 km^2, with the chief source being the municipal wastewaters (15 MT/year/12,000 km^2), rather than the storm water plus dry weather flow or the washout fluxes (1 and 5 MT/year/12,000 km^2, respectively). Extraction studies indicated that the silver in these sediments occurred predominantly as sulfides or bound to the organic phase.

The concentrations of silver in the wastewater particulates were 32 to 130 (average 70) mg/kg compared with about 6 mg/kg for the sediments in the basins receiving them. (The sediments were collected at 75 to 890 m from the sewage outfalls.)

High concentrations of mercury, silver, chromium, and zinc were recently found in the sediments downstream from the Vint Hill Farms Station military reservation. Although the sediment contamination extends for two miles in South Run in eastern Fauquirer County, Virginia, which runs into Lake Manassas, the Manassas water treatment plant is able to remove the metals because of the water insolubility of the chemical forms present. There is concern, however, about heavy metal bioaccumulation in fish (Toxic Materials News, 1978).

The silver concentration in sediments is important because bottom-feeding mollusks, etc., tend to concentrate silver. Luoma and Jenne (1977) in laboratory studies determined that the uptake of silver, bound to various typical sediment species--by the clam _Macoma_ _balthica_, depended on the particular sediment species to which it was bound. The concentration factor for sediment-bound ^{110m}Ag (dry clam tissue/dry sediment) was 3.667 to 6.140 from calcite; 0.395 to 0.850 from MnO_x; 0.043 to 0.146 from Fe_xO_y; 0.034 to 0.076 from biogenic $CaCO_3$; and 0.028 to 0.030 from organics. The percent of ^{110m}Ag in the soft tissues of the clam was 42.6 to 57.0 (average 54.4 percent). In these experiments, the sediment-bound silver contributed somewhat more silver to the clam tissue than did solute silver (0.034 to 0.552 mg/kg versus 0.004 to 0.135 mg/kg in soft tissues).

Of 380 finished waters, 6.1 percent were found to contain silver at concentrations varying from 0.3 to 5 μg/l (mean 2.2 μg/l). Table 3 shows the silver content of water supplies for several U.S. cities. The silver content of these water supplies did not exceed the U.S. drinking water limits for maximum allowable concentration of silver, 0.05 mg/l (Kopp, 1969). In another study, the maximum concentration of silver found in 2,595 distribution samples from 959 public water supply systems was 26 μg/l. The average silver content found in waters having pH $\leq$ 8 was 0, while for those at pH $\geq$ 8.0, the average silver content was 1 μg/l. Of Chicago water samples, 15 percent showed increased concentrations of silver after leaving the water treatment plant (McCabe, 1970).*

In 1935, Braidech and Emery reported 0.010 to 0.200 mg/kg silver (average 0.080 mg/kg) in the solid residues of all 24 city water supplies they studied. The highest value was from Denver, Colorado.

*Silver contents in distribution samples (i.e., tapwater) may be higher than the finished water from the treatment plant because of the preferred use of tin-silver solders for joining copper pipes in the home, office, or factory. In addition, American Standard, Inc. connects copper pipes for hot and cold water with tin-silver solder during the assembly of kitchen and bathroom appliances (Silver Institute, 1976b).

TABLE 3

Silver in City Water Supplies

Ag Content (ppb)	Location	Remarks	Reference
0.23 (7.0 maximum)			Cannon & Hopps, 1971
50 (maximum)	U.S.	Maximum allowable Ag content of drinking water according to Federal Water Poll. Con. Admin.	Kopp & Kroner, 1970
8 (average) 30 (maximum observed)	U.S.	2,595 samples of 956 municipal water supplies.	Taylor, 1971
ND - 0.35	Birmingham, AL		Durfor & Becker, 1962
0.09	Mobile, AL		Durfor & Becker, 1962
ND - < 0.31	Montgomery, AL		Durfor & Becker, 1962
≤0.53 - ≤0.92	Phoenix, AZ		Durfor & Becker, 1962
ND - ≤ 0.54	Tucson, AZ		Durfor & Becker, 1962
ND - ≤0.40	Long Beach, CA		Durfor & Becker, 1962
≤0.3	Los Angeles, CA		Durfor & Becker, 1962
≤0.4 - ≤0.7	Los Angeles, CA		Bargmon & Garber, 1973
≤0.06	Oakland, CA		Durfor & Becker, 1962
≤0.1 - ≤0.2	Sacramento, CA		Durfor & Becker, 1962
≤0.78	San Diego, CA		Durfor & Becker, 1962
≤0.06 - ≤0.08	San Francisco, CA		Durfor & Becker, 1962
≤0.32	San Jose, CA		Durfor & Becker, 1962
ND - ≤0.26	Denver, CO		Durfor & Becker, 1962
0.29	Hartford, CT		Durfor & Becker, 1962
≤0.14 - 0.30	New Haven, CT		Durfor & Becker, 1962
≤0.25 - ≤0.28	Washington, DC		Durfor & Becker, 1962
ND - ≤0.49	Jacksonville, FL		Durfor & Becker, 1962
ND - ≤0.50	Miami, FL		Durfor & Becker, 1962
ND - ≤0.21	St. Petersburg, FL		Durfor & Becker, 1962
0.55	Tampa, FL		Durfor & Becker, 1962
≤0.03 - 0.07	Atlanta, GA		Durfor & Becker, 1962
≤0.05 - ≤0.26	Savannah, GA		Durfor & Becker, 1962
≤0.26 - ≤0.34	Honolulu, HI		Durfor & Becker, 1962
0 - 9 (100%) 0 - 1 (74%) 2 - 5 (22%)	Chicago, IL distribution points (maximum 2 ppb at the treatment plants)		McCabe, 1969
≤0.2 - ≤0.27	Chicago, IL		Durfor & Becker, 1962
≤0.5 - ≤0.59	Rockford, IL		Durfor & Becker, 1962
≤0.29	Evansville, IN		Durfor & Becker, 1962

TABLE 3 (Continued)

Ag Content (ppb)	Location	Remarks	Reference
0.2 - <0.54	Fort Wayne, IN		Durfor & Becker, 1962
≤0.24	Gary-Hobart, IN		Durfor & Becker, 1962
ND - 0.39	Indianapolis, IN		Durfor & Becker, 1962
≤0.24 - ≤0.48	South Bend, IN		Durfor & Becker, 1962
≤0.30	Des Moines, IA		Durfor & Becker, 1962
≤0.2 - 0.3	Louisville, KY		Durfor & Becker, 1962
≤0.30 - 0.80	Baton Rouge, LA		Durfor & Becker, 1962
≤0.25 - 7.0	New Orleans, LA		Durfor & Becker, 1962
≤0.18 - 0.24	Shreveport, LA		Durfor & Becker, 1962
≤0.13 - 0.74	Baltimore, MD		Durfor & Becker, 1962
0.18	Boston, MA		Durfor & Becker, 1962
0.14 - 0.49	Springfield, MA		Durfor & Becker, 1962
0.06	Worcester, MA		Durfor & Becker, 1962
0.21 - 0.22	Detroit, MI		Durfor & Becker, 1962
≤0.25 - ≤0.53	Flint, MI		Durfor & Becker, 1962
≤0.23 - ≤0.25	Grand Rapids, MI		Durfor & Becker, 1962
≤0.15 - 0.48	Minneapolis, MN		Durfor & Becker, 1962
≤0.17 - ≤0.34	St. Paul, MN		Durfor & Becker, 1962
0.68	Jackson, MS		Durfor & Becker, 1962
≤0.28 - ≤0.56	Kansas City, MO		Durfor & Becker, 1962
≤0.22 - ≤0.23	St. Louis, MO		Durfor & Becker, 1962
0.3	St. Louis, MO	Finished Water	
≤0.41	Lincoln, NE		Durfor & Becker, 1962
≤0.46	Omaha, NE		Durfor & Becker, 1962
≤0.09	Jersey City (contiguous with Paterson and Newark)		Durfor & Becker, 1962
0.09 - 0.38	Newark, NJ		Durfor & Becker, 1962
≤0.09 - 0.09	Paterson, NJ		Durfor & Becker, 1962
ND - ≤0.5	Albuquerque, NM		Durfor & Becker, 1962
0.07 - 0.12	Albany, NY		Durfor & Becker, 1962
≤0.26	Buffalo, NY		Durfor & Becker, 1962
0.23 - 0.39	New York City, NY		Durfor & Becker, 1962
≤0.14 - 0.30	Rochester, NY		Durfor & Becker, 1962
≤0.19	Syracuse, NY		Durfor & Becker, 1962
0.32 - ≤0.41	Yonkers, NY		Durfor & Becker, 1962
≤0.04 - 0.17	Charlotte, NC		Durfor & Becker, 1962
≤0.17	Akron, OH		Durfor & Becker, 1962
≤0.29	Cincinnati, OH		Durfor & Becker, 1962
0.23	Cleveland, OH		Durfor & Becker, 1962
ND - ≤0.26	Columbus, OH		Durfor & Becker, 1962
1.1	Dayton, OH		Durfor & Becker, 1962

TABLE 3 (Continued)

Ag Content (ppb)	Location	Remarks	Reference
≤0.16	Toledo, OH		Durfor & Becker, 1962
≤0.23	Youngstown, OH		Durfor & Becker, 1962
0.54 - ≤0.76	Oklahoma City, OK		Durfor & Becker, 1962
≤0.19 - ≤0.20	Tulsa, OK		Durfor & Becker, 1962
≤0.02	Portland, OR		Durfor & Becker, 1962
≤0.26	Erie, PA		Durfor & Becker, 1962
≤0.15 - ≤0.17	Philadelphia, PA		Durfor & Becker, 1962
≤0.12 - ≤0.19	Pittsburgh, PA		Durfor & Becker, 1962
0.07	Providence, RI		Durfor & Becker, 1962
ND - ≤0.24	Chattanooga, TN		Durfor & Becker, 1962
ND - 0.19	Memphis, TN		Durfor & Becker, 1962
≤0.16	Nashville, TN		Durfor & Becker, 1962
ND - ≤0.29	Austin, TX		Durfor & Becker, 1962
0.15 - ≤0.29	Dallas, TX		Durfor & Becker, 1962
ND - ≤0.86	El Paso, TX		Durfor & Becker, 1962
ND - ≤0.15	Houston, TX		Durfor & Becker, 1962
ND - 1.5	Lubbock, TX	A well	Durfor & Becker, 1962
≤0.27 - ≤0.54	Salt Lake City, UT		Durfor & Becker, 1962
≤0.10 - ≤0.15	Norfolk, VA		Durfor & Becker, 1962
≤0.10	Richmond, VA		Durfor & Becker, 1962
0.05 - ≤0.06	Seattle, WA		Durfor & Becker, 1962
0.26 - 0.53	Spokane, WA		Durfor & Becker, 1962
≤0.05	Tacoma, WA		Durfor & Becker, 1962
≤0.5	Madison, WI		Durfor & Becker, 1962
≤0.24 - ≤0.25	Milwaukee, WI		Durfor & Becker, 1962

In a survey of metal concentrations in the drinking (tap) waters of Canadian communities, silver was found in 0.1 percent of the 239 sampled waters (detection limit of neutron activation analysis was 0.001 to 0.005 µg/l) (Neri, et al. 1975).

Tapwater in the Boston metropolitan area contained $\leq$ 0.010 mg/l silver in 896 samples although Cu, Zn, Pb, and Fe were often present in the soft water of the area due to the corrosion of pipe materials (Karalekas, et al. 1976).

Silver is used to purify potable water for Swiss ski resorts, German Breweries, soft drink bottlers, British ships, Shell Oil Company tankers, drilling rigs, and over half the world's airlines including Pan Am and American. In the United States, the number of companies registered by the U.S. EPA to produce silver-containing water filters grew from 2 to 19 by February, 1978, from 10 only two years before. At least one water filter has been widely promoted by television advertising in the United States for home use. The units of Katadyn Products, Ltd. in Switzerland either produce silver ions anodically or by the slight dissolution of metallic silver impregnated on fine-porosity ceramic filters. They have been approved by the Swiss government for 38 years, requiring less than 200 µg/l for their antimicrobial action (Silver Institute, 1976a, 1977b, 1978).

The Soviets have found silver ions at concentrations of 100 to 200 µg/l to be safe, stable, and long-lasting for purification of polluted water for drinking in the Soviet space ship and orbiting station program. After animal tests showed these concentrations to be nondetrimental, year-long human volunteer studies confirmed the results (Silver Institute, 1973b). Silver sterilizers producing

100 to 200 µg/l silver ions were also used on the Apollo Spacecraft waste and potable water systems (Albright, et al. 1967).

Ingestion from Food

Silver is a normal trace constituent of many organisms (Boyle, 1968). The ash of higher plants ususally is found to contain $\leq$ 1 ppm silver, while the ash of terrestrial plants, in general, usually contains about 0.2 ppm silver. Higher values occur in trees, shrubs, and other terrestrial plants near regions of silver mineralization. Seeds, nuts, and fruits generally have higher silver contents than other plant parts (Smith and Carson, 1977).

Snyder, et al (1975) estimated that the average intake of silver by humans is 70 µg/day. Kehoe, et al. (1940) had determined that daily dietary intake of humans in the U.S. was 88 µg/day. Tipton, et al. (1966) found the average daily intake of silver in the diets of men and women in the U.S. were 35 µg and 40 µg silver, respectively. Hamilton and Minski (1972/1973) determined that the average daily human dietary intake of silver in the United Kingdom was 27 ± 17 µg. No consideration was given to intake from water used for cooking foods, making beverages, or drinking. Clemente, et al. (1977) reported that the average silver intake in the diets of three Italian populations was 0.4 µg/day as determined by neutron activation analysis. Five-day fecal samples of the population which had a silver intake of up to 7 µg/day showed a range of 1.1 to 202 µg/day (average 30 µg/day). Some source of pollution was felt to be the cause of greater metal intake. The latter population came from a large town in central Italy, whose major source of pollution was automotive engine exhaust.

Murthy and Rhea (1968) of the U.S. Public Health Service in Cincinnati measured, by atomic absorption analysis, 0.027 to 0.054 mg/kg (average) silver in cows milk collected as market samples from various U.S. cities. The silver content did not vary significantly between cities, but there was a significant difference between quarterly sampling periods in the southeastern states. The national weighted average was 0.047 ± 0.007 mg/kg. Milk from 32 cows on farms serving Cincinnati contained 0.037 to 0.059 mg/kg silver (average 0.047 ± 0.006 mg/kg). Table 4 lists the silver concentration in several food items.

^{110m}Ag is an activation product produced during nuclear fission. The concentration factors* from Lichen to caribou or reindeer estimated by Hansen, et al. (1966, cited by Garner, 1972) for ^{110m}Ag in muscle were 0.3; for liver, 80; for kidney, 1.3; and for bone, 3. Beattie and Bryant (1970) had estimated that 15 percent of the total ^{111}Ag dose from activation products would be received in a 30-year period starting in infancy by the forage-cow-milk pathway.

Sewage-sludge amended soils may have 10 times or more silver than normal and may increase human intake of silver by its incorporation into food crops in greater than normal amounts. Silver uptake by plants appears to be directly related to its soil concentration (Cooper and Jolly, 1969). Addition of phosphate to soil contaminated with silver, however, reduces its plant availability (Dawson, 1974).

*Ratio of ^{110m}Ag activity per unit wet weight of tissue activity per unit wet weight of lichen.

TABLE 4

Silver in Some Foods

Type of Food	Silver Concentrations, mg/kg	Reference
Beef	0.004-0.024	Armour Research Foundation, 1952; Mitteldorf and Landon, 1952
Beef liver (SRM 1577)	0.005-0.194 (same sample by three laboratories)	Masironi, 1974
Pork	0.007-0.012	Armour Research Foundation, 1952
Mutton and lamb	0.006-0.011	Armour Research Foundation, 1952
Milk powder	0.010 ± 0.04	Schelenz, 1977
Potato powder	0.015 ± 0.005	Schelenz, 1977
Sugars		Hamilton and Minski, 1972/1973
Brown (Barbados)	0.03	
Demerara	0.004	
Refined	0.001	
Granulated	0.002	
Mollusks	0.1-10.0 (dry weight)	Boyle, 1968; Cooper and Jolly, 1970
Crustaceans	2.0 (dry weight)	Boyle, 1968
Trout (Lake Cayuga, New York)	0.48-0.68 (dry weight)	Tong, et al. 1974
Mushrooms	"Up to several hundred" (dry weight)	Cooper and Jolly, 1970
Wheat (*Triticum* spp.)	0.5 (dry weight)	Kent-Jones and Amos, 1957
Bran	1.0 (dry weight)	
Flour	0.4 (dry weight)	
Coffee beans	0.02 (dry weight)	Vanselow, 1966
Tea (*Camellia sinensis*)	0.20-2.00 (dry weight)	Vanselow, 1966

It is possible that the silver content would be increased in the meat of animals pastured or fed grains raised on contaminated soils.* At least one study, however, has indicated that the transfer of iron, copper, nickel, chromium, zinc, cadmium, and lead from sewage-sludge amended soils to dairy or beef cattle milk or tissues is minimal (Nelmes, et al. 1974).

Among aquatic species harvested for food, the heptopancreas and nephridial organs of brachiopods, molluscs, and arthropods, particularly crustaceans, accumulate heavy metals. The glandular tissue of the liver of fish and all other vertebrates concentrates metals (Vinogradov, 1953). Marine animals accumulate silver in concentrations which are higher than their environment. Clams and scallops growing near municipal sewage-sludge dumping sites accumulate higher concentrations of silver than do those growing where the concentrations of silver are lower (Toxic Materials News, 1975). The enrichment factor calculated by Noddack and Noddack (1939) for silver in marine animals over seawater is 22,000. A bioconcentration factor is not estimated from the value since these data are not purported for indigenous species. The dead bodies of animals in reducing environments will contribute their silver to sediments, a major factor in the biogeochemical cycle of silver (Boyle, 1968).

Besides food and drinking water, silver is possibly ingested from dissolution of silver dental amalgams in the mouth by saliva. Wyckoff and Hunter (1956) qualitatively detected silver spectrographically in the erythrocyte contents and possibly in the plasma and erythrocyte membrane (ghosts) of two people who had dental fillings. No silver was detected in a preliminary examination of another person who did not have any dental fillings. Reynolds and Warner (1977) concluded that the corrosion product of Ag_3Sn amalgams after only 30-minute exposure to human saliva _in vitro_ was $SnCl_4$.

---

*If a 0.25-lb portion of meat contains 0.007 mg/kg, the 0.0065 mg silver consumed would represent only about 1 to 2 percent of the low silver dietary intake reported by Tipton, et al. (1966).

Some silver may be released to soft tissues from silver amalgam dental fillings when placed in unlined cavities according to Leirskar (1974), who found by atomic absorption analysis that there was definite release of zinc and mercury into a human monolayer epithelial cell culture (22 μg Zn/ml and 0.0177 to 0.0196 μg Hg/ml); some silver also appeared to have been released. Silver amalgam cultures contained 0.02 μg Ag/ml after three days. (The detection limit for silver, however, was 0.01 μg/ml--much higher than that for mercury.) Leirskar cited three other studies that reported diffusion of amalgam constituent metals, including silver, into adjacent dentin.

Inhalation

Silver is generally a very minor constituent of ambient aerosols. Table 5 gives a reasonably representative sample of silver determinations in air, although it is by no means exhaustive, since reports of nuclear activation analyses of atmospheric particulates are proliferating rapidly. Interestingly enough, Chadron, Nebraska, which has a population of 6,000 in a sparsely inhabited region, had the same average ambient air concentration of silver in 1973--0.15 ng/m^3--as San Francisco had in 1970. A nonindustrial

TABLE 5

Silver in Ground-Level Atmospheric Aerosols 6,7

City	Date	Aerosol Silver Concentration ng/m^3	Aerosol Silver Concentration ppb	Reference
Heidelberg, Germany	April - June, 1971	4.2	0.0032	Bogen, 1974
Niles, MI	June, 1969	1	0.00077	Bogen, 1974
Northwest IN	1969	1.5		Dams, et al. 1971
East Chicago, IL	June, 1969	2.4	0.0019	Bogen, 1974
Chicago, IL	1968	4.3		Brar, et al. 1970
Oak Ridge, TN Vicinity: Walker Branch Watershed	July, 1974	0.17	0.00013	Andren, et al. 1974
Chadron, NE	1973	average 0.15 (range 0.02 to 1.8)		Struempler, 1975
	June - Sept. 1973	0.14		
	June - Sept. 1974	0.04		
Washington, DC	1974	1.1		Trout, 1975 cited by Greenberg, et al. 1978
San Francisco, CA	1970	0.15		John, et al. 1973 cited by Greenberg, et al. 1978
Kellogg, ID (city hall)		10.5* (range 0.936 to 36.5)		Ragaini, et al. 1977

*Average Concentrations of mercury, antimony, cadmium, zinc, and lead ranged from 113 to 10,800 ng/m^3. The nearby Bunker Hill smelter smelts silver-rich lead concentrates and roasts zinc concentrates.

city, Washington, D.C., had a concentration of 1.1 ng/m^3 in 1974. The very industrialized urban environment of Chicago, Illinois, had an ambient atmospheric silver concentration only four times higher (4.3 ng/m^3). Even one of the sites having an expectedly high silver concentration in the silver-rich Coeur d'Alene region of northern Idaho had only an order of magnitude greater silver concentration (average 10.5 ng/m^3) than a nonindustrialized large population center.

Smith and Carson (1977) estimated that total annual atmospheric silver emissions in the United States in the early 1970's were about 340 short tons or about 310,000 kg. About 60 percent of this total was distributed equally between iron and steel production and cement manufacture, about 12 percent each was due to fossil fuel burning and nonferrous metal smelting and refining, and about 7 percent was due to urban refuse incineration. Another published estimate for total annual silver emissions was 417 short tons (Dulka and Risby, 1976, citing a personal communication from V. Duffield, 1975).

Greenburg, et al. (1978) attributed to urban refuse incineration a much higher share of the total silver content in the urban particulate load. They estimated that the contribution of silver from refuse incineration to ambient urban air is 1.7 ng/m^3.

Steel mills have been implicated as the major source of aerosol silver, yet the following data (Harrison, et al. 1971) do not seem to support this contention. Air particulate samples were collected on June 11 and 12, 1969, at 25 stations in the northwest Indiana area, including the Hammond-East Chicago-Gary-Whiting metropolitan complex. At that time, the entire sampling area contained three large steel mills, as well as four large petroleum refineries, foundries, steel fabricators, chemical plants, a large cement-manufacturing plant, and two large power utilities. The silver concentrations in the area ranged from 0.5 to 5 ng/m^3. The maximum silver concentration was found at a station downwind from the steel mills. High silver concentrations did not occur at the same stations where maximum iron levels occurred. Therefore, steel manufacturing was not believed to be the major source of silver found in these samples (Dams, et al. 1971).

At another station, in Gary, near the third steel mill, secondary maxima for iron and eight other metals were associated with a silver concentration of 4 ng/m^3. The direction of the unusually strong, steady wind prevailing during the sampling was such that most of the shoreline steel and cement plant emissions (~85 percent and 12.5 percent, respectively, of the area's industrial particulate emissions) may have been swept directly over the lake so that the observed air concentrations at stations nearest them were much lower than normal (Dams, et al. 1971). On April 4, 1968, one day after general rainfall, with wind blowing at 34 km/hr, the silver concentrations in surface air samples from 22 aerosol-collecting stations in Chicago, Illinois, ranged from 0.18 to 7.0 ng/m^3 (average 4.3 ng/m^3). Correlation coefficients for silver with other elements or dust were not determined (Brar, et al. 1970).

Another source of silver to ambient air is from volatile emission from certain trees. Curtin, et al. (1974/1975) traced the path of elements from the soil and mull (the humus-rich layer of mixed organic and mineral matter 3 to 8 cm thick beneath individual trees) into the needles, twigs, and volatile exudates of Lodgepole pine, Engelmann spruce, and Douglas fir in Idaho Springs, Colorado and Stibnite, Idaho. Silver was not detected in the soil; but in Colorado, its highest concentrations were in the mull ash under all species. In Idaho, the silver concentration was highest in the twigs of the pine and spruce and in the exudate residue of the Douglas fir. Presumably, the metals in the exudate are complexed by terpenes and appear in the blue haze of forested areas.

Nadkarni and Ehmann (1969) measured 2.61 mg/kg silver in a reference cigarette tobacco* by neutron activation analysis and 2.87 mg/kg silver in the paper. Nadkarni, et al. (1970) found 0.27 ± 0.18 mg/kg silver in a filter cigarette of a popular brand and 0.18 ± 0.03 mg/kg in a nonfilter cigarette of the same brand; there was 0.48 mg/kg silver in 1.65 g of smoke condensate from 500 filter cigarettes and 0.30 mg/kg silver in 14.5 g condensate from 500 nonfilter cigarettes. Only 0.60 percent of the silver transferred into the mainstream smoke condensate of the filter cigarette; 4.4 percent transferred from the nonfilter cigarette. The amount of silver inhaled into the lungs in the mainstream smoke per cigarette would be negligible according to these data: 8.7 ng per nonfilter cigarette and 1.6 ng per filter cigarette.

*A blend of four major tobacco types: flue-cured, Burley, Oriental, and Maryland. The nonfilter cigarette dimensions were 85 mm in length, 25 mm in circumference.

Exposure from cloud-seeding operation may be significant only to a ground-based generator operator.* Standler and Vonnegut (1972) estimated the concentration of silver (0.1 μm particles) in air downwind in the target area from a ground-based silver iodide cloud-seeding generator is 0.1 ng/m^3, a factor of 10^5 below the maximum allowable concentration in workplace air. At the generator site itself, however, exposure exceeds the maximum permissible concentration within 50 m downwind of the generator. Seven cloud-seeding operators with extensive exposure to silver iodide knew of no persons who had experienced any ill effects due to silver iodide, despite the fact that their hands may remain yellowed for weeks. Vonnegut, however, recalled a technician in New Mexico in the early 1950's who claimed the aerosol from a ground-based generator aggravated his respiratory allergy, and Douglas had reported in 1970 a skin rash developing in an individual who had been within a few meters of an operating generator for six hours. Inhaling the acetone vapors from the unignited silver iodide solution is of more concern to some operators.

The Occupational Safety and Health Administration (OSHA) standard for silver metal and soluble compounds in the workplace air is 0.01 mg/m^3 for an 8-hour time-weighted average (39 FR 23541).

According to the American Conference of Governmental Industrial Hygienists (ACGIH, 1977), the Threshold Limit Value-Time Weighted Average (TLV-TWA) for aerosol silver metal or soluble silver compounds as metal is 0.01 mg/m^3. The tentative value for the Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) is 0.03 mg/m^3. The TLV-TWA is based on a normal 8-hour workday or 40-hour work week, day-after-day exposure. The TLV-STEL is defined as the maximum concentration to which a worker may be exposed continuously for as long as 15 minutes without irritation, chronic or irreversible tissue changes, or sufficient narcosis to increase accident proneness, self-rescue, or work efficiency. Up to four such excursions may occur per day provided at least 60 minutes elapse between such exposures and provided the TLV-TWA was not exceeded in the time lapses.

---

*Bernard Vonnegut in 1947 in General Electric Laboratory experiments, showed that silver iodide crystals can initiate ice crystal formation (Fleagle, et al. 1974).

The ACGIH (1971) stated that, "If one assumes a 20-year exposure, a 10 m^3/day* respiratory volume, and a 50 percent body retention, a level of silver fivefold the recommended TLV (0.05 mg/m^3) will result in an accumulation of 1.2 g or a probable borderline amount for the production of argyria."** The problem of how absorption of metallic silver from the lungs might parallel direct injection of silver compounds into the bloodstream was not dealt with.

More pertinent information with regard to a TLV for silver in air was supplied to the ACGIH by Fassett in a personal communication (undated and unidentified as to organization). After observing silver workers for many years, he believed that silver concentrations of 0.01 mg/m^3 in workroom air are unlikely to cause argyria.

---

* Presumably, for the work day. Snyder, et al. (1975) estimated a 23 m^3/day respiratory volume.

**The reference is somewhat in error in stating that the gradually accumulated intake of from 1 to 5 g Ag will lead to generalized argyria. The values given by Hill and Pillsbury (1939) are 0.91 to 7.6 g, given i.v.

Jindrichova (1962, cited by ACGIH, 1971) had observed 12 cases of argyria resulting from exposure to workroom air concentrations of 1 to 2 mg/m^3 in the processes of manufacturing silver varnish and its use in silvering radio-technical parts.

Winell (1975) compared the hygienic standard for chemicals in the work environment for which both the United States and the USSR had standards. Since silver was not included, apparently the USSR does not have a limit for silver. Argentina, Great Britian, Norway, and Peru apply the U.S. standards.

Occupations where silver inhalation is still possible include silver polishers and occupations involved in melting silver or its low-melting alloys (e.g., tin-silver solder for copper plumbing). The silver nitrate manufacturers and packers were the most frequent victims of generalized argyria according to Harker and Hunter (1935), but the processes have been obsolete for decades.

Silver polisher's lung was first described in 1945. The dust inhaled contains both iron oxide (rouge) and metallic silver. The latter stained the tissue black (Aponte, 1973). Argyria was seen less often in pourers of molten silver than in silversmiths engaged in filing, soldering, polishing, engraving, etc. But, according to Lewin (1896), it was always localized rather than generalized as would occur from inhalation. Yet Koelsh (1912) (both references cited by Harker and Hunter, 1935) found that two men whose occupation involved cutting up thin sheets of silver had generalized pigmentation and suggested it was due to inhalation or ingestion of the workplace dust (300 mg silver/kg dust).

In the melting area at the San Francisco mint on December 24 to 27, 1972, the Industrial Hygiene Services Branch of the National Institute for Occcupational Safety and Health (NIOSH) determined 0.01 to 0.04 mg/m^3 of silver fumes in the air (average 0.02 mg/m^3; the threshold limit value of 0.01 mg/m^3 was exceeded in seven of the eight samples). The melting and casting operations caused smoke and fumes throughout the melting room despite adequate ventilation over the melting area (Anania and Seta, 1973). Although silver is seldom encountered in new U.S. coinage except for the special silver-containing editions of U.S. Eisenhower dollars made only at the San Francisco mint from time to time, such information is probably applicable to the extent of occupational exposure at firms that make medallions, silver bars, and other commemorative items of case silver. Sterling silverware and holloware are generally manufactured without melting operations. Silver platers are more at risk from cyanide poisoning rather than silver poisoning.

Dermal

Laws in many states still require that a few drops of a 1 or 2 percent silver nitrate solution be applied to the conjunctiva of the eyes of newborn infants to prevent ophthalmia neonatorum by transmittal of gonorrhea from the mother (Martin, 1965). Use of silver nitrate is a legal requirement in Denmark, but it is not used in Japan or Australia. Elsewhere, there is a free choice between silver nitrate and antibiotics. Silver nitrate is no longer used in 20 percent of U.S. hospitals because of the dangers of chemical conjunctivitis (Shaw, 1977).

In the U.S., several silver-containing pharmaceuticals for use on skin or mucous membranes can be obtained; some do not need a prescription. Among the medications are Argyrol® (mild silver protein) and Protargol® (strong silver protein), Neo-Silvol® (colloidal silver iodide in a gelatin base), silver nitrate, and Silvadene® (silver sulfadiazine) (Pariser, 1978).

The risk of argyria from silver-containing topical medicinals continues today. Marshall and Schneider (1977) reported a case of systemic argyria which had first begun to appear by November, 1971 in a 46-year-old woman. She had begun using silver-nitrate applicators for bleeding gums from ill-fitting dentures, upon the advice of her dentist. From April, 1970, she had used three applicators per week and continued using them even after the first bluish discoloration appeared about her nose and forehead. By July, 1972, she was already strikingly pigmented, was diagnosed as having argyria, and was advised to discontinue use of the applicators. In 1973, the pigmentation of her abdominal organs was noted during an exploratory laparotomy. None of the patient's physical ailments was attributed to the use of silver nitrate.

Moyer and his associates instituted the use of hypotonic silver nitrate burn treatment in April, 1964, at Barnes Hospital in St. Louis, Missouri. It was discontinued there in December, 1967. Monafo had developed colloidal silver isotonic solutions, and Margraf and Butcher had developed other silver salts in ointment. In the opinion of Monafo and Moyer (1968) of St. John's Mercy Hospital in St. Louis, "Because most salts of silver, other than the nitrate, are insoluble..., it was predicted that due to precipitation at the wound surface, little or no absorption of silver would occur through burn wounds. It was, therefore, anticipated that systemic toxicity would be inconsequential. Moreover, argyria, the slate-gray discoloration of the skin that results from the ingestion or absorption of silver is innocuous physiologically and does not shorten life." No patient had developed argyria, but silver was detected in plasma and urine. Patients with extensive burns treated for up to 80 days had 0.05 to 0.30 mg silver per liter in their plasma.

Hartford and Ziffren (1972) reported on the results of 0.5 percent silver nitrate use on the dressings of 220 burn patients. Compared with the rate in the 1950-1960 decade, mortality had been dramatically reduced. By the late 1960's, the search for a less soluble but effective silver compound lead to the synthesis (by C.L. Fox, Jr.) and clinical trials of silver sulfadiazine.

Silver sulfadiazine, by 1974, according to Fox (1975), had been used in the treatment of more than 10,000 burn patients in many countries for more than seven years. It had been approved by the regulatory agencies in the United States and the United Kingdom so that more general use had begun (Silver Institute, 1977a).

Less than 10 percent of the sulfadiazine is absorbed, and far less of the silver. Daily treatment of 1 m^2 of burn surface (a 50 percent burn in an adult) requires 200 g $AgNO_3$ (127 g Ag) (40 liters of 0.5 percent solution) or 4 g silver sulfadiazine (1.2 g Ag) (one 400 g jar of 1 percent cream or lotion). Fewer than 10 of 10,000 patients showed any drug sensitivity (Fox, 1975).

A 1 percent silver cream made of silver nitrate, zinc sulfate, and allantoin has been developed for self-care treatment of cutaneous ulcers. In a study of 400 chronic skin ulcers in 264 patients, 84.5 percent were completely healed within 3 to 40 weeks (10 weeks average) (Silver Institute, 1977c). The compound is another slow-release form of silver and is less likely to produce argyria than silver nitrate preparations alone.

Silver nitrate hair dyes have been used regularly since about 1800. Sodium thiosulfate developers are added to the hair first, followed by 0.5 to 15 percent silver nitrate solutions containing various amounts of ammonia to give gradations of shade. The 5 percent solution with ammonia is widely used to dye eyebrows and eyelashes and is the only colorant commonly used for the purpose in the U.S. (Wall, 1957, 1972). At least one case of argyrosis has been reported from such use. An Italian physician who dyed his eyebrows, moustache, beard, and eyelashes with a silver dye for 25 years developed argyria in the conjunctiva of both eyes (Wall, 1957).

Several swimming pools in the U.S. are equipped with filtering systems of activated carbon of very high surface area coated with pure metallic silver. The effective water concentrations of silver ions are 20 to 40 μg/l (Silver Institute, 1973a,c, 1974, 1976c). Dermal absorption of silver from swimming pools is not expected, although absorption through the conjunctiva is possible. Although evidence is cited later in this document that mucous membranes and wounds allow absorption of silver compounds to an unknown extent,* very little, if any, ionic silver is absorbed by intact skin.

PHARMACOKINETICS

Absorption

Silver may enter the body via the respiratory tract, the gastrointestinal tract, mucous membranes, or broken skin. Some reports even claim absorption through intact skin. In most cases of argyria, caused by occupational exposure, absorption has been via the respiratory tract or the conjunctiva (Hill and Pillsbury, 1939). Up to 10 percent of a single oral dose of silver is absorbed. The literature data do not lend themselves to a ready calculation of the degree of absorption after inhalation or dermal exposure. Absorption from even nonintact skin appears to be much less than 1 percent.

Rats ingesting 1.68 g/kg of colloidal silver for 4 days or 0.42 g/kg for 12 days showed higher silver concentrations in the lungs than in the liver. Based on distribution studies described in the following discussion, the amount found in the lungs is so high that perhaps the rats aspirated part of the dose. Otherwise, the total amount of silver recovered in the heart, lungs, kidney, spleen, liver, and muscles would indicate that at least 2 percent of the higher dose (if one assumed the average rat weighed 200 g) was absorbed. Apparently, almost 5 percent of the silver was absorbed at the lower dose (Dequidt, et al. 1974).

*That is, the percent of the total dose absorbed has not been calculated; however, long-term use of the topical silver medicinals (generally silver nitrate) for mucous membranes has certainly led to argyria.

Scott and Hamilton (1950) concluded that rats absorbed 0.1 percent of a carrier-free dose of radiosilver upon ingestion.* Rats were given the doses intragastrically. Four days after the dosing, 99.0 percent of the original dose had been eliminated in the feces and 0.18 percent in the urine; yet the tissue distribution apparently totals 0.835 percent; 0.52 percent in the lungs, 0.025 percent in the blood, 0.11 percent in the G.I. tract, 0.034 percent in the skin, and 0.076 percent was in the balance remaining after the other internal organs, bones, and muscles revealed no silver.

Dogs (four male beagles, average 5.5 years, 12 to 16 kg) were presumed to absorb 10 percent of oral doses of 0.6 μCi ^{110}Ag as the nitrate since only 90 percent was lost very rapidly (Furchner, et al. 1966b).

Three rabbits inhaled an aerosol of 10 percent colloidal silver solution for eight hours (Kondradova, 1968a,b) and were immediately sacrificed. In the tracheal epithelium, silver had accumulated in the large vacuoles in the cytoplasm of epithelial cells.

In a human who had accidentally inhaled ^{110m}Ag, most of the inhaled silver had a biological half-life of about one day, probably due to rapid mucociliary clearance, swallowing, and fecal excretion. By whole-body counting on the second day, silver activity was seen in the liver, which indicated some absorption although the published data do not permit a calculation of absorption (Newton and Holmes, 1966). Newton and Holmes believed colloidal forms of silver are the species of silver absorbed in the lungs and that phagocytosis would account for the localization in the liver. They cited a study by Hahn and Corrothers (1953) in which the radiosilver coating of colloidal gold particles administered intrabronchially to dogs was gradually leached off in the lungs and appeared in the liver.

---

*Furchner, et al. (1966b) state that the findings of the Scott and Hamilton report indicate about 4 percent absorption from the gastrointestinal (G.I.) tract. They found that mice absorbed less than 1 percent.

West, et al. (1950) reviewed early investigations into cutaneous absorption of silver. Muller, in a privately printed 1936 report cited in Hill and Pillsbury (1939), stated that all of the silver oxide in a 5 percent oily dispersion was absorbed after topical application to intact skin, wounds, or mucous membranes. He found no silver deposits in the skin or underlying tissue, but he claimed to have accounted for 73.1 to 88.5 percent of the silver administered to four guinea pigs in their excreta within 31 days of the inunction of their intact skin. Win (1887) could find no permanent deposit of silver granules six weeks after their dermal injection. Jacobi (1878) could not produce generalized argyria, however, by s.c. injections of a silver solution in rabbits; yet Pincussen and Roman (1931) found silver in blood, skin, kidney, spleen, and liver after s.c. injection of silver sulfate in rats. West, et al. (1950) citing unpublished data of West, Elliott, and Hahn, found activity in many organs and feces of albino rats after s.c. injections of a mixture of ^{108}Ag and ^{110}Ag.

Hill and Pillsbury (1939) reviewed several studies in which silver was apparently not absorbed from intact skin. The Muller study was described in a footnote.

The depilated backs of rats were painted daily with a saturated solution of Collargol® (colloidal silver and silver oxide) for three months. By atomic absorption spectrometry and colorimetry, traces of silver were found in the heart and lungs, 1.54 mg/kg in the kidney, 1.50 mg/kg in the spleen, and 0.16 mg/kg in the liver (Dequidt, et al. 1974).

Wahlberg (1965) determined that the absorption of silver nitrate from a solution containing 25.8 g Ag/l by the intact skin (3.1 cm^2) of guinea pigs was less than 1 percent five hours after topical application.

Argyria was relatively common following use of silver preparations as applications to the mucous membranes according to Hill and Pillsbury (1939), but the argyria was usually described as "local" rather than "generalized," which would indicate systemic absorption.

Marshall and Schneider (1977), however, have described a rare, present-day case of generalized argyria due to assiduous use of a silver nitrate stick for bleeding gums due to ill-fitting dentures.

Applications of silver nitrate dressings to open wounds allows systemic absorption of silver. Constable, et al. (1967) treated open wounds (3.5 x 3.5 cm^2) on the backs of guinea pigs with 0.5 percent $AgNO_3$ solution for five days. In Table 6, the range of silver concentrations in the organs of four or five topically treated guinea pigs are compared with those in one guinea pig drinking the

TABLE 6

Comparison of Tissue Distribution after Dermal Gastro-Intestinal Absorption of Silver from a 0.5 Percent $AgNO_3$ Solution*

Organ	Concentration, mg/kg Dermal Route	Gastrointestinal Route
Skin	3.0-35.5	1.5
Skin by wound	42.5-3,491.1	-
Ulcer	2.0-6,649.5	-
Liver	15.2-29.6	35.3
Bile	0.5-1.8	0
Kidney	7.6-152.0	2.1
Lymph node	1.8-14.4	2.8
Stomach	2.2-24.9	164.8
Intestine	3.8-38.0	10.0

*Source: Constable, et al. 1967.

0.5 percent $AgNO_3$ solution (probably not the same amount as received by topical treatments). Loss of silver from the liver was fairly rapid after cessation of treatments. After one week, <40 percent remained and after two weeks, <25 percent. Since the $AgNO_3$ contained some ^{111}Ag ($t_{1/2}$ = 7 days), radioautographs showed that silver was concentrated in the Kupffer cells and around the bile canaliculi with very small amounts in the glomeruli and most in the kidney in the cells lining the renal tubules.

Bader (1966) analyzed the organs of two burn patients who had been treated with fresh dressings of silver nitrate continuously for at least six days or for every 8 hours for 30 days. In the 66-year-old man, who had died of a brain tumor about 50 days after the 8-hour treatment was initiated, the silver concentrations in the tissues wer slightly above normal: bone, 0.025 mg/kg; heart, 0.040 mg/kg; kidney, 0.140 mg/kg; and skin, 2,800 mg/kg. The second patient was an 18-year-old male, who died of respiratory complications on his 7th hospital day. Before death, the silver concentration in his urine was 0.038 mg/l and in his blood, 0.12 mg/l. There was no silver detected in his lungs or brain; but the concentrations in other tissues were: heart, 0.032 mg/kg; kidney, 0.14 mg/kg; spleen, 0.23 mg/kg; liver, 0.44 mg/kg; muscle, 2.0 mg/kg; and skin, 1,250.0 mg/kg. On the basis of information of Fox (1975), the daily dose of silver from silver nitrate dressings is 127 g. The patient dying on the 7th day was probably treated for at least six days, receiving 762 g silver. On the assumption that his body weight and the weight of his organs were those of reference man (Snyder, et al. 1975) and with the exclusion of the silver content of his skin, one can calculate that the organs named contained 57.5 mg silver. Because the silver concentration of his liver and heart were approximately the same as those of the older man, we will assume that his bones had the same silver content, 0.9 mg. These values plus his urinary output for at least one day (certainly no more than 0.04 mg and probably less because of possible renal impairment), total 58.44 mg or 0.008 percent of the 762 g dose of silver.

Silver sulfadiazine has very low water solubility and probably remains in the wound exudate according to Nesbitt and Sandman (1977). The solubility in distilled water cannot be detected by any potentiometric method. At pH 3.851 with a nitric acid buffer, ionic strength 0.1 M, the solubility of Ag^+ was about 6.5×10^{-5} M; at pH 2.128, about 60×10^{-5} M. Yet, Wysor (1975a), citing a Marion Laboratories brochure on Silvadene® dated March 1, 1972, stated that very large concentrations of silver sulfadiazine applied topically has caused silver deposition in the kidney basement membrane. Wysor (1975a) gave CF_1 mice, infected with Plasmodium berghei, oral doses of 1,050 mg/kg of various silver sulfonamides for five days. Only silver sulfadiazine proved effective in curing the mice of their malaria; presumably, it was solubilized and absorbed.

Dermal absorption of silver sulfadiazine from wounds is low. In clinical trials with silver sulfadiazine cream, Fox, et al. (1969) reported that when 5 to 10 g of the drug was applied to the burned surface of 31 patients, the levels of sulfadiazine in the blood were 10 to 20 mg/l and there was 60 to 300 mg/l in the urine (24-hour excretion of 100 to 200 mg). When burned guinea pigs were treated with radioactive silver sulfadiazine, Fox, et al. (1969) did not detect any radioactivity in the organs or blood.

Moncrief (1974) reported that 10 percent of the sulfadiazine of silver sulfadiazine applied to burns is absorbed to give blood levels of 15 to 40 mg/l, peaking 3 to 4 days after initiation of treatment. The daily absorption rate decreases during the first 10 to 15 days after the initiation of therapy. Radiosilver does not appear in the blood from silver sulfadiazine; but when silver nitrate soaks are used, there is 0.05 to 0.3 mg/l silver in the plasma.

Burke (1973) compared the excretion of silver by children and adults, untreated and treated with silver sulfadiazine. His results are in Table 7.

Distribution

The amount of silver administered, its chemical form, and the route by which it is administered affect the tissue content and distribution of silver within the body (Furchner, et al. 1968). It is retained by all body tissues. The primary sites of deposition in persons who have never taken silver therapeutically are the liver, skin, adrenals, lungs, muscle, pancreas, kidney, heart, and spleen. Silver is also deposited in blood vessel walls, testes, pituitary, nasal mucous membrane, maxillary antra, trachea, and bronchi (Sax, 1963). Although silver does not accumulate in the lungs with age, it was present in 39 percent of the lungs from Americans analyzed by Tipton and Cook (1963). Examinations of accidental death victims indicated that the silver content of the myocardium, aorta, and pancreas tended to decrease with age (Bala,

TABLE 7

Silver Concentrations in Human Blood and Excreta*
(mg/kg)

Subject	Blood	Urine	Feces
Patient with 70 percent burns, treated with silver sulfadiazine for 1 month	0.75	0.73	3.2
Same patient, 2 months later, after grafting	0.13	0.12	19.3
Patient with 60 percent burns, treated with silver sulfadiazine for 3 months, off treatment for 1 month	0.09	0.02	1.0
Control adult	0.05	0.003	0.53
Child with 15 percent burns, 11-months-old (length of silver treatment not given)	-	7.0	6.0
Control child	-	2.0	0.21

*Source: Burke, 1973

et al. 1969). Silver accumulates in the body with age, however, even if none is administered intentionally (Hill and Pillsbury, 1939).

A striking feature of argyria is the regular deposition of silver in blood vessels and connective tissue, especially around the face, conjunctiva, hands, and fingernails (Hill and Pillsbury, 1939). The silverbearing particles in one case of localized argyria of a photoprocessor were found to be silver sulfide (Ag_2S), possibly contained in the mitochondria (Buckley, et al. 1965). The silver-containing particles were sparsely distributed at the dermo-epidermal junction of the papillary bodies adjacent to the epidermal portion of the sweat ducts. The silver had entered the skin via the sweat glands (Buckley, 1963).

In argyria, aside from the blood vessels and connective tissues, the dermis of the skin, glomeruli of the kidney, choroid plexus, mesenteric glands, and thyroid contain the greatest amounts of deposited silver. The epithelium is free of silver deposits (but Buckley, et al. 1965, report that silver ions are present there).* Other tissues where deposition may occur include: bone marrow, pancreas, liver, spleen, testes, and ovaries (Hill and Pillsbury, 1939; Sax, 1963; Van Campen, 1966). The adrenals, lungs, dura mater, bones, cartilage, muscles, and nervous tissue are minimally or never involved as deposition sites for silver (Hill and Pillsbury, 1939). Exposed skin shows greater amounts of melanin in the dermis and epidermis. Robert and Zurcher (1950, cited by Lever, 1961), had stated that silver favors melanin formation by increasing oxidative processes. Silver is especially deposited in intima of blood vessels and connective tissue of internal organs. Basement membranes around the acini of the testes and of the choroid plexis are rich in silver granules (Harker and Hunter, 1935).

---

*According to Lever (1961) in the 3rd edition of Histopathology of the Skin, in argyria, silver is found in the dermis--chiefly outside the cells, as uniformly sized particles ("...fine, small round, brownish...")--but never the epidermis. The particles, lying singly or in clumps, are $< 1\mu$ in diameter. "Under a dark-field microscope, the silver appears as brilliantly refractile, white granules against a dark background." Melanin and hemosiderin granules are larger, largely intracellular, and nonrefractile on dark-field illumination.

Polachek, et al. (1960) reported the metabolism of radiosilver in a patient with malignant carcinoid that agreed reasonably well with the carrier-free silver rat studies of Scott and Hamilton (1950). The radiosilver was incubated with the patient's own blood and was first associated most with the erythrocytes and the globulin fraction of the plasma (77 percent in the globulin, 15 percent in the albumin, and 8 percent in the fibrinogen fractions). Upon injection (i.v.) into the patient (with 0.002 mg carrier Ag/kg), the 43 μCi radiosilver was removed rapidly from the blood, presumably by the liver with biologic half-life of 48 days. At seven minutes after injection, only 30 percent of the injected dose remained in the blood; at two hours, 10 percent remained; and at 1 to 20 days, 2 percent. Urinary excretion was 5 percent of fecal excretion. Excretion was much slower than in the rat studies. Only 0.5 to 3 percent of the original dose was eliminated in each of seven 24-hour periods in the first 21 days post-administration. Urinary excretion in these 24-hour periods ranged from 0.03 to 0.29 percent.

The patient lived 195 days after the injection. Analysis of the organs post-mortem showed the highest concentrations (counts per minute per gram) in: liver, 70.0; skin, 37.7*; kidney (left), 10.0; brain, 9.2; and kidney (right), 7.5. From 4.0 to 5.6 cpm/g was found in an abdominal lymph node, an adrenal gland, the primary carcinoid in the ileum, a testis, the aorta, and the pancreas; and 2.2 to 3.8 cpm/g was found in the urinary bladder, prostate, heart, stomach, rib, and ileum. Smaller concentrations were found in the carcinoid in the liver (metastatic), a lung, muscle, and the spleen (Polachek, et al. 1960).

Intramuscular injections of dextrin-protected radiosilver colloid left much material at the injection site, but an i.v. dose in albino rats (1 ml contained 1.72 x 10^6 cpm) was mainly found in the reticuloendothelial system. The bone content was primarily in the marrow. The continued presence of activity in the blood suggested that tissue-deposited silver was being translocated. A gelatin-protected silver colloid injected i.v. into albino mice was also deposited in highest concentrations in the reticulondothelial system; 22 hours after i.p. injection of the gelatin-protected silver colloid into five albino mice, 36.5 percent of the activity was in the gastrointestinal tract and contents; 16.5 percent in the liver; 10.2 percent, in muscle; 3.5 percent, in bone; and 0.4 percent, in the skin (except the head) (Gammill, et al. 1950).

Table 8 adapted from Smith and Carson (1977) reviews some other animal data on early distribution of injected silver compounds.

---

*Because of its relative weight, the skin had the highest accumulation of silver.

TABLE 8

Silver Distribution in Animal Tissues

Organism	Organ	Form of Ag	Distribution at								Dosage	Remarks	Reference
			10 min.	30 min.	1 hr.	3 hr.	6 hr.	24 hr.	2 days	7 days			
White mice	Blood	$^{110}Ag^{125}I$	19.7%		13.5%	15.2%	0	0	0	0	0.2 ml i.v. of 50-60 μg/ml in tail vein	Ag also found in lungs, kidneys, small intestine, intestine, bladder, muscle, testesm, and brain.	Anghileri, 1969
	Liver		65.6%		48.3%	40.7%	44.3%	30.9%	20.0%	10.11%			
	Spleen		0.35%		0.70%	0.60%	0	0	0	0			
	Stomach		0.51%		0.92%	1.25%	0	0	0	0			
	Thyroid		0		0.02%	0	0	0	0	0			
	Bone		0.42%		0.31%	0.51%	0.93%	0.01%	0	0			
		Total	86.58%		63.75%	58.32%	45.25%	30.91%	20.0%	10.11%			
White mice	Blood	$^{110}Ag^{82}Br$		0.82%	1.12%			0.56%			0.2 ml i.v. of 50-60 μg/ml in tail vein	Results indicate Ag is released in an insoluble form and not as Ag^+ Radiosilver is slowly excreted through bile and urine.	Anghileri, 1969
	Liver			58.7%	63.6%			26.1%					
	Spleen			0.34%	0.18%			2.09%					
	Stomach			0.73%	0.57%			0.41%					
	Thyroid			-	-			-					
	Bone			0.21%	0.14%			0.45%					
		Total		60.80%	65.61%			23.61%					
						2 hr.							
Rats	Lungs	$^{110}AgNo_3$ at pH 5.0 in 0.05 M acetate buffer				Found							Anghileri, 1969
	Kidneys					Found							
	Heart					Found							
	Pancreas					Found							
	Small intestine					Found							
	Large intestine					Found							
	Bladder					Found							
	Muscles					Found							
	Testes					Found							
	Brain					Found							
Rats	Blood	$AgNO_3$ and $^{64}Cu(NO_3)_2$ injected into in vivo ligated segments of the G.I. tract.									0.01 μmoles Cu^{2+} in 0.4 ml distd. H_2O with 1.5, 3.0, and 6.0 μmoles Ag^+	Ag had little effect on uptake of Cu except that a significantly greater proportion of Cu was deposited in the liver and significantly less retained by the blood in Ag-treated rats.	VanCampen, 1966
	Heart												
	Kidneys												
	Liver												
	Spleen												

Deposition of carrier-free radiosilver in rats was similar after i.m. and i.v. injections. The most interesting information from the studies of Scott and Hamilton (1950) was the distinct difference in organ accumulation between carrier-free doses and doses containing stable silver compound added as carrier. Table 9 shows the difference in distribution six days after i.m. injections when three rats per group were given carrier-free silver or radiosilver with 0.1 mg stable silver (0.4 mg/kg) or with 1.0 mg stable silver (4.0 mg/kg).

Obviously, the liver had difficulty maintaining its efficient removal of silver at a dose of 0.1 mg/rat, but the dose of 1.0 mg/rat definitely showed the limitation of its capacity so that the rest of the reticuloendothelial system had to handle much more silver. At the highest dose compared with the carrier-free dose, the liver had accumulated 94 times as much of the absorbed dose of silver; the spleen, 269 times as much; and the skin, 31 times as much. Other organs, including the kidney, had about 10 times as much silver. Scott and Hamilton presumed that a dose of 5 mg silver per kg i.m. would be required to give a tissue distribution similar to that seen in classical argyria.

West, et al. (1949, 1950), had shown that ^{111}Ag nitrate when injected i.m. or i.v. "...is taken up by blood leukocytes and

TABLE 9

Distribution of Silver in the Rat at Day 6 Following Intramuscular Injections of Different Doses of Silver (percent of dose per organ)*

	Dose		
	Carrier-Free	0.1 mg	1.0 mg
Percent of Dose Absorbed	92.1	63.7	53.5
Absorbed			
Heart and lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.50	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
G.I. tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33
Unabsorbed	7.9	36.3	46.5

*Source: Scott and Hamilton, 1950.

carried into inflammatory body areas."* Presumably, the Ag-protein complexes formed were phagocytized. Since insoluble silver compounds would be less corrosive and also phagocytized, West and Goldie (1956), injected normal and tumor-bearing mice with $^{111}Ag_2O$ to examine the distribution of the radioactivity by autoradiographs. In normal Swiss albino mice given s.c. injections of 0.1 or 0.2 mCi $^{111}Ag_2O$, the activity 24 hours after the injection remained mostly at the injection site with a large fraction in the liver and minor amounts in the spleen, stomach, colon, kidney, and lung. In normal mice given the injections i.p., most of the activity was in the liver; some remained at the injection site, but absorption was much higher than by s.c. injection. Thus, higher activity was seen in each of the organs than with s.c. injections. However, mice with tumors (Sarcoma 180, Sarcoma McGhee, Carcinoma C_3H/BA, and Carcinoma EO771) showed by far the major activity in the tumors and intracavity exudates when injected with radiosilver near the tumor site (s.c. into the tumor periphery, into the pleural cavity with malignant growth, or into the peritoneal cavity bearing malignant growth). West and Goldie (1956) explained the preferential silver absorption by tumors as follows: a s.c. injection in normal mice remained largely at the injection site, presumably clogging the lymphatics. When adjacent tumors were present, they apparently absorbed the $^{111}Ag_2O$ into macrophages and interspaces of malignant tissue.

---

*West, et al. (1950) found that up to 10 percent of intradermal injections of labeled silver nitrate ($^{108,110}Ag$) remained at the injection site after 72 hours. When Staphylococcus aureus was injected simultaneously in the same leg five times as much silver was found at the injection site after 72 hours. But if injected in different legs, the activity was preferentially found at the site of bacterial injection.

In argyric rats given 0.5 percent silver nitrate in their drinking water for nine months, silver was especially found in lysosomes of the liver's Kupffer cells, at the basal membrane of the capillaries, and the connective tissue cells of the pancreas. In the parenchymatous cells, Putzke (1967) found silver only as a lipoid-silver complex or in lipofuchsin-like lysosomes and in residual bodies. The lysosomes were thought to be responsible for intracellular transport and the extrusion of silver. In the liver, there was increased activity of cytochrome oxidase, but marked decrease in the activity of succinate dehydrogenase.

Ham and Tange (1972) cited numerous studies wherein silver nitrate was administered in the drinking water of rats to study glomerular basement membrane formation. These authors gave drinking water containing 2,500 mg/l $AgNO_3$ for 12 weeks to albino and hooded female rats, killing pairs of animals at 1 to 12 weeks to study the tissues by light and electron microscopy. Other pairs of animals were killed at 1 to 10 months after silver intake. Four of each strain were also killed for study 16 months after the cessation of silver intake. As shown in Table 10 the silver content in the liver was similar in both strains, but varied by strain and individuals of the same strain in the kidneys. Abnormalities in glomerular epithelial and endothelial cells were not progressive or consistent. Bloom, et al. (1959) cited by Ham and Tange (1972) in

TABLE 10

Silver in Formalin-Fixed Rat Tissues After Drinking Silver-Containing Water, mg/kg* **

	Hooded Rats		Albino Rats	
	Liver	Kidney	Liver	Kidney
3 Months' intake of silver at 2,500 mg/l in drinking water	6.8, 7.0	6.1, 9.8	6.3, 7.0	3.7, 7.1
10 Months after removal of silver from drinking water	1.4, 2.8	3.7, 4.3	2.2, 2.5	1.8, 3.4
16 Months after removal of silver from drinking water	0.8-1.4	2.7-4.1	0.7-1.6	3.0-6.0

* Source: Ham and Tange, 1972.

**Determined by potentiometric titration.

observing the phenomenon of increased formation of basement membrane thought the increase might be greater than normal thickening due to aging.

Moffat and Creasey (1972) fed 10 adult rats and 3 adult rabbits drinking water containing 1,500 mg/l $AgNO_3$ for 4 to 20 weeks to study the permeability of medullary vessels of the kidney to protein. Only the rat kidney showed heavy silver deposits in the glomeruli and outer medulla basement membranes. Both species had heavy deposits in the inner medulla, but the distribution differed markedly. In the rat, most of the silver was in the basement membrane of the vessels and loops of Henle, but the heaviest deposits were around the descending vasa recta. The main deposits in the rabbits were also in the vessels and loops of Henle, but the distribution in each vessel or loop was asymmetrical. Most of the silver was deposited on the side adjacent to the collecting duct. In the silver-dosed rats, the occurrence of degenerating kidney cells was more common than in normal rats.

Creasey and Moffat (1973) also cited several studies in which silver nitrate had been administered in drinking water to experimental animals to study the basement membranes of some (brain, eye, and renal glomeruli) of the many kinds of tissues in which silver accumulates. Silver is carried in the blood as a silver-protein complex, and its deposition in tissues appears to indicate vascular permeability to protein. Extravasation of protein in the kidneys occurs in immature rats (younger than three months) much less than in adults. This was shown by the slower rate of appearance (12 to 14 weeks versus 5 weeks) and finer particulate size ($<$30 nm versus

30 to 90 nm) of silver granules deposited in the kidneys of immature rats given 1,500 mg/l $AgNO_3$ solution for 4 to 15 weeks after weaning, as compared with adults on the same regimen. The increasing amount of silver deposited in the rat kidney glomeruli with age has also been attributed to increasing glomerular filtration rate.

Silver granules were detected by electron microscopy in the glomerular basement membrane of random-bred adult mice after 12 days of ingesting drinking water containing 6 mM $AgNO_3$ (648 mg/l Ag). After 14 weeks of silver ingestion, larger aggregates were observed in the basement membrane and mesangium. Within 21 weeks after cessation of silver ingestion, the silver deposits did not change significantly (Day, et al. 1976). Some of the mice were used in a study of immune complex glomerular disease induced by i.p. injections of bovine serum albumin. The silver-labeled basement membrane helped determine that the immune deposits were on the intracapillary aspect of the basement membrane (Hunt, et al. 1976).

Metabolism

Silver is transported in the protein fractions of the plasma, especially the globulins. The reticuloendothelial system, especially the liver, handles most of the removal of absorbed silver from the body at moderate doses (0.4 mg/kg in rats, according to Scott and Hamilton, 1950). At higher doses, deposits are markedly increased in the skin. Inhaled silver particles that are not removed from the lungs by the mucociliary reflex and coughing are probably phagocytized and ultimately removed to the liver, from which they are eventually excreted via the bile. Formation of silver selenide deposits in the liver may be another method of detoxifying silver (the interactions of silver and selenium are discussed under Synergism and/or Antagonism). Many studies have focused on elucidating the chemical forms of the silver deposits in the skin. The most probable forms are metallic silver, silver sulfide, or silver complexes with the sulhydryl amino acids in proteins. Since the deposits are so inert, they cannot be removed by common heavy metal detoxification procedures. These deposits appear to be another method of detoxification by the organism. In the kidney, complexation with metallothionein may be another detoxification pathway.

Transport of silver in the blood is largely in the globulin fraction. None of the silver content of blood is dialyzable "to any extent" through cellophane (Scott and Hamilton, 1948). In vitro, the distribution of carrier-free ^{105}Ag after three days in heparinized rat blood containing an equal volume of isotonic saline was: hemoglobin, 8.4 percent; ghosts of the cells, 11.6 percent; globulin, 64 percent; albumin, 16 percent; and the protein-free fraction, 0.001 percent. In vivo, the distribution of total amount of radiosilver activity in rat blood five minutes after i.v. injection was erythrocytes, 10.2 percent; globulin, 57 percent; albumin, 32 percent; and the protein-free fraction, 0.7 percent; the liver already contained 86 percent of the injected dose by five minutes (Scott and Hamilton, 1950).

Lifshits (1965) reported the distribution of endogenous silver in the blood of 16 healthy humans (in mg/l whole blood). In the plasma, the fibrinogen fraction contained 0.0018 mg/l; the globulins, 0.0064 mg/l; the albumins, 0.0024 mg/l; and minerals, 0.0014 mg/l. In the erythrocytes, the silver distribution was: stroma, 0.0038 mg/l; nonhemoglobin proteins, 0.0009 mg/l; and erythrocyte minerals, 0.

Silver iodide is readily broken down by biological tissues. Anghileri (1968) injected 0.2 ml of $Ag^{131}I$ (0.23 mg AgI/ml and 10 μCi ^{131}I/ml) into the tail veins of young albino mice (15 to 20 g). In a similar experiment, the silver portion of the molecule was labeled (^{110}Ag). Less radioactivity was observed in the liver with ^{110}AgI than with $Ag^{131}I$ (53 percent versus 70 percent of the injected dose after 10 minutes), but the ^{110}Ag radioactivity remained longer in the liver (21 percent versus 4.1 percent at 24 hours). The concentration of radioactivity was much higher in the stomach and thyroid with ^{131}I than with ^{110}Ag in the injected silver iodide during the first 24 hours.

Camner, et al. (1974) reported that silver-coated 5 μm Teflon® particles were phagocytized in vitro by rabbit alveolar macrophages in the presence of serum more slowly than were similar particles coated with aluminum or chromium and at about the same rate as were particles coated with manganese or uranium. When serum was not added, there was less difference in phagocytization rates. The former case is more comparable with the in vivo situation. (For silver, the average number of particles phagocytized per macrophage in the presence of serum after 1.5 hours was 0.58;

and for aluminum, 0.72. Without serum, the numbers were 0.38 and 0.40, respectively.) There were fewer than 4 percent nonviable macrophages after the 1.5-hour exposure of a monolayer of macrophages from disease-free rabbits to the particle suspension in 75 percent Parker 199 solution and 25 percent autologous rabbit serum or in 100 percent Parker 199 solution.

After daily applications of 1 percent silver sulfadiazine cream to the abraded skin of albino rabbits for 100 days at dosages of 5.0, 10.0, or 15.0 g/kg/day, the kidney tissues were treated with various solvents* in an effort to determine the chemical form of the silver deposit. Sulfadiazine was not detected in chloroform extracts of acidified tissue homogenates.** Since only the strongly oxidizing solvent 16M nitric acid dissolved any of the kidney tissue silver deposits (the range of silver concentrations in four rabbit kidneys by atomic absorption spectrometry was 172.3 to 247.0 mg/kg), Grabowski and Haney (1972) concluded that the form of silver was as a silver tissue complex whose dissociation under normal conditions would be minimal, and whose only physiological threat would be mechanical interference to kidney function. No structural damage or impairment had been noted in the kidneys, however.

---

* 16M HNO_3, 30 percent NH_4OH, 50 percent CH_3CO_2H, 9 percent H_2NCSNH_2, 37.5 percent HCl.

**The sulfadiazine probably remained in the acid solution as a salt: $A^- \, {}^+NH_3C_6H_5SO_2NHC_4N_2H_3$.

Pariser (1978), using the differential solubility methods* of Buckley, et al. (1965), found that only cyanide solutions removed the silver from tissue sections of argyric patients (ages 83, 58, and "elderly"). This suggested that the chemical form of silver was as silver sulfide or some other highly insoluble complex rather than metallic silver.

Chromatographically purified metallothionein from normal rat liver contained significant concentrations (by neutron activation analysis) of Cd, Zn, Cu, Hg, and Ag. Experiments with $^{110m}Ag^+$ showed further incorporation into metallothionein (Sabbioni and Girardi, 1977). Possibly this is the mechanism whereby the kidneys excrete bound silver.

Excretion

Regardless of route and chemical form administered, fecal excretion of silver always predominates over urinary excretion. Most absorbed silver is excreted into the intestines by the liver via the bile.

Scott and Hamilton (1950) showed that the liver is the chief organ responsible for elimination of absorbed silver. The silver content in the liver, feces, and gastrointestinal tract contents was reduced when bile duct ligation or light chloroform anesthesia (which produces liver damage) in rats was performed prior to injection of carrier-free radiosilver. Ordinarily, after i.m. injection of 1 µCi radiosilver (0.1 µg), 60.9 percent of that absorbed was excreted in the feces on the first day, and 21.4 percent was already in the gastrointestinal (G.I.) tract. After bile duct ligation, on day 2, 57.6 percent of the activity still remained in the liver, 5.06 percent was in the G.I. tract, and only 6.85 percent was in the feces. After light chloroform anesthesia for three hours, the rats excreted silver at 0.0001 the normal rate.

---

*Tissues were extracted with thiosulfate fixing bath (dissolves silver mercaptides, oxides, chlorides, bromides, iodides, carbonates, and phosphates); ferricyanide-bromide bleach followed by thiosulfate fixing bath (dissolves metallic silver); and 5 percent sodium cyanide (which dissolves most insoluble silver salts such as silver sulfide).

Urinary excretion of silver is generally very low. At four days after an intravenous (i.v.) dose of radiosilver, rats had excreted 94.06 percent of the dose in the feces and 0.34 percent in the urine and at 16 days, 97.8 percent and 1.8 percent, respectively (Scott and Hamilton, 1950). Administration of Ca EDTA, a common metal chelating agent, reportedly increased urinary excretion of silver. Ligating the bile duct in laboratory animals increased renal excretion while reducing fecal excretion by a factor of 10, thereby further demonstrating the biliary nature of silver excretion (Furchner, et al. 1968). Radiosilver (^{110}Ag) iodide was removed from the blood two hours after i.v. administration and was slowly excreted through the bile and urine in a nonionic form (Anghileri, 1971). The ratio of urinary-fecal excretion is 0.001 to 0.258 (Furchner, et al. 1968; Kalistratova, et al. 1966; Anghileri, 1969).

Dequidt, et al. (1974) found significant silver excretion in the urine after several i.p. injections of different forms of silver medicinals. Wistar rats given 12.6 mg/kg silver i.p. as the nitrate daily for five weeks (apparently a 4-day work week) eliminated 10 to 20 µg/rat/day in the urine. At 5 mg/kg/day silver as silver nitrate for 24 injections within six weeks the urinary silver excretion was 3 to 15 μg/rat/day (average 4 μg). When injections of 29.6 mg/kg colloidal silver were given to rats 11 times within three weeks, the urinary excretion was 8 to 24 μg/rat/day (average 12.6 μg). Colloidal silver i.p. injections at 5 mg/kg/day for 24 injections within six weeks gave urine containing 2 to 10 μg/rat/day. Silver proteinate i.p. injections (16 within 4 weeks) at 5 mg/kg gave urinary silver contents of 3 to 15 μg/rat/day.

In rats, silver is eliminated from the lungs in two or three phases. The fastest phase (0.3 to 1.7 days) removes most of the inhaled dose by mucociliary clearance. A second phase and third phase remove absorbed silver, mostly via the liver, with half-lives of about 8 to 15 and 40 to 50 days, respectively.

As of 1964, ^{110m}Ag had been detected 583 times in 186 different individuals in the nuclear industry. Sill, et al. (1964) described the inhalation exposure of 50 people to activation product ^{110m}Ag when an experimental loop containing silver-soldered thermocouples in the Engineering Test Reactor was opened. Reexposure occurred during cleanup procedures, complicating data interpretation; but the calculated effective half-life was about eight days before recontamination. The source of the ^{110m}Ag and the time of exposure was not the same for all subjects. The individual with the highest body burden of 0.93 μCi had an elimination rate with a half-life of 13 days. Two others had effective half-lives of 17 and 69 days. (The International Commission on Radiological Protection gives 4.9 days for whole-body elimination half-life.)

In most cases, maximum activity occurred in the nose, mouth, chest, and lower edge of the rib cage. In almost all the cases, ^{110m}Ag could not be detected in 1,500-ml urine samples (Sill, et al. 1964).

At Harwell, England, a 29-year-old man accidentally inhaled dust from an experimental hole in a nuclear reactor. The burden of radionuclides was below the maximum permissible, but the levels of ^{65}Zn and ^{110m}Ag allowed prolonged study of their retention and distribution (Newton and Holmes, 1966). Whole-body gamma-ray spectrometry on the second day after the accident showed 197 nCi ^{110m}Ag (and 330 nCi ^{65}Zn). By day 6, 90 percent of the zinc still remained, but only 40 percent of the silver seen on day 2 remained. About 25 percent of the total activity appeared to be confined to the region of the liver. The ^{110m}Ag appeared to be more closely confined to the liver than was the ^{65}Zn on day 16, when individual measurements were made. For 155 days, after which the silver distribution studies were abandoned, the liver was the major site of deposition. The whole-body effective half-life of the 15 percent retained silver was 43 days (biological half-life 52 days).* During the first 100 days, the content in the liver appeared to decrease at about the same rate, but there was a longer-lived component that may have been an artifact from ^{137}Cs. There was no silver in the urine during the first 54 days, but it was present in fecal samples up to about day 300.

---

*Polachek, et al. (1960) had reported a value of 48 days for liver clearance. The International Commission on Radiological Protection in 1959, however, quoted a value of 15 days.

The M.S. theses of Phalen (1966) and Garver (1968) reported controlled inhalation studies in which rats were exposed, nose only, to ^{110m}Ag-tagged silver smoke. Clearance from the body was described in two exponential functions of biological half-lives, 8 days and 20 days, indicating two separate body pools of silver (Phalen and Morrow, 1973).

The initial rapid clearance from the lung is on the order of several hours or one or two days (Phalen, 1966; Garver, 1968; Skolil, et al. 1961; and Newton and Holmes, 1966). In humans, 80 percent was cleared from the lungs with a biological half-life of one day. The half-life for the remainder in the Skolil, et al. (1961) report was 15 days (Phalen and Morrow, 1973).

Phalen and Morrow (1973) studied six female beagle dogs who received single acute inhalation exposures to ^{110m}Ag-tagged silver aerosol via tracheal tubes (for 7 to 15 minutes while anesthetized). The method of aerosol generation (by wire explosion) insured well-characterized spherical particles, primarily of metallic silver. The activity median aerodynamic diameters were 0.5 μ. Absolute deposition in the lungs was 1 μg/kg (in text; in the author's abstract the value given is 1 mg/kg).

The solubility rate constants were: in distilled water, 0.1 $\mu g/cm^2/day$ at 35 to 37°C; and in simulated interstitial fluid, 10 $\mu g/cm^2/day$. One could expect 99 percent of the aerosol mass in the lung to dissolve in two days.

The activity appeared to clear at about 6 to 8 hours. One dog, exposed for 15 minutes, was sacrificed six hours post exposure. There was 96.9 percent of the initial deposit still in the lungs, 2.4 percent in the liver, 0.38 percent in the blood, and 0.02 percent in the stomach. The solubility rate constant in the lung was calculated to be 1 μg/cm^2/day. Perhaps some dissolved silver remained in the lung as a tissue complex. By three days, half of the initial amount deposited was gone. Since only 20 percent appeared in the excreta during the first five days, most of the silver was not removed by the mucociliary mechanism. Perhaps 90 percent was carried by the blood to the liver. For three dogs, the major silver repositories were the liver, lungs, brain, skin, and muscle; one of the dogs had larger amounts in bile, liver, and bone (Table 11).

Where larger particles are inhaled, elimination may more resemble that observed after oral dosing, when much of the lung deposit has been eventually swallowed.

Camner, et al. (1977) found that inhaled 4-μm Teflon® particles coated with carbon, silver, or beryllium were cleared from rabbits' lungs (8 to 10 New Zealand rabbits per test) at about the same rate during the first week, despite differences in their toxicity and in the rates of in vitro phagocytosis that had been reported. Presumably, intact particles of the size and lung burden used (aerosol inhaled for only 6 to 8 minutes, resulting in 1 to 10 μCi and 10 to 100 μg deposition) were not actively removed from the lungs by the alveolar macrophages during the first week after inhalation. External measurements of clearance could be made because all of the particles were tagged with ^{51}Cr.

The silver-coating remained 50 percent intact in rabbit serum (replaced daily) at 37°C for 12 days. But in a flow-through system

TABLE 11

Biological Half-Lives ($t_{1/2}$) in Days for Clearance in 4 Dogs After Inhalation of Silver Aerosol*

	Lung			Liver		Body
Pooled Data	$t_{1/2}$	$t_{1/2}$	$t_{1/2}$	$t_{1/2}$	$t_{1/2}$	$t_{1/2}$ by analysis of excreta (1% in urine)
Dogs 1, 3, 4, and 5	1.7	8.4	40	9.0 (97% of that excreted)	40	8.4 - 12.9

*Source: Phalan and Morrow, 1973.

with 10 percent horse serum in saline at 37°C for eight days, 26 percent of the particles had lost more than half their coatings.

Kent and McCance (1941) followed the excretion of silver for three separate 7-day periods in a woman with severe generalized argyria produced by "washing out her nose for many years with an organic silver preparation." Her negative balances (Table 12) may have been due to desquamation of the silver-containing cells from the alimentary canal lining.

Enders and Moench (1956) reported that argyric albino rats with varying degrees of heavy silver deposits in the liver and very weak to heavy deposits in the kidney after consumption of a silver medicinal (Targesin®) for three months, showed progressively less silver in these organs after the silver feeding had been stopped. At three months postexposure, the liver deposits in 10 rats were only very weak or entirely absent; and there were no deposits in the kidneys and duodenum. After six months on a normal diet, four of the nine rats showed very weak silver deposits in liver, kidney, and/or duodenum.

Buckley and Terhaar (1973) reported that the skin is an excretory organ in generalized argyria with gradual translocation of silver from the general body pool through the dermis and finally into the epidermis as soluble silver. One worker with generalized argyria was studied. Silver appeared to be released from melanin-silver complexes as a soluble ionic form near the surface of the epidermis.

In rats, mice, and rabbits, 99 percent of a one-time oral dose of silver is eliminated within 30 days. Dogs, which absorb 10

TABLE 12

Silver Balance in a Female With Severe Generalized Argyria*

Silver, mg/week	Week 1	Week 2	Week 3
Food	0.05	0	0.7
Feces	1.3	1.5	2.3
Urine	0	0	0
Balance	-1.25	-1.5	-1.6

*Source: Kent and McCance, 1941

percent of the dose, require more than 28 days. Snyder, et al. (1975) for the International Commission on Radiological Protection reviewed the literature pertaining to the silver balance for reference man and concluded that his intake in food and fluids is 70 µg/day and his losses include 9 µg/day in urine, 60 µg/day in feces, 0.4 µg/day in sweat, and 0.6 µg/day in hair.

Tipton and Stewart (1970) reported that the range of silver found in the ash of food was 0.5 to 75 mg/kg; of feces, 1 to 115 mg/kg; and urine, 0.0 to 15 mg/kg (analysis by spectrographic procedures).

Kehoe, et al. (1940) found only 0.06 mg/silver/day eliminated in the feces, which was less than the 0.088 mg/day dietary intake of silver. Although silver was detected in the blood of Americans, Frenchmen, Mexicans, and Germans, it was not detected in their urine. Almost all silver is excreted in the feces of mammals with only traces in the urine (Gammill, et al. 1950; Scott and Hamilton, 1950). However, silver may be detected in urine in cases of silver poisoning (Sunderman, 1973). Silver has also been detected in nasal and vaginal secretions (Barsegyants, 1967).

Analyses for silver were made on diets and excreta of a husband (Subject B) and wife (Subject A) for 30 days. Subject B had a mean intake of 0.035 mg silver per day and Subject A, 0.04 mg silver per day, respectively. Subject A drank five cups of coffee (not analyzed for silver content) per day, had a fecal/urinary silver excretion ratio of 3, and a positive average silver daily balance of 0.007 mg/day (2.6 mg/yr). Subject B drank three glasses of milk per day (analyzed for silver content), had a fecal/urinary excretion ratio of 8, and a negative average daily silver balance of 0.054 mg after 30 days (Tipton, et al. 1966).*

Average human intake from the diet is estimated at up to 0.088 mg/day (Kehoe, et al. 1940). At that rate, if 100 percent of the silver ingested is retained in the body, approximately 31 years would be required to accumulate 1 g of silver. Based on the data of Tipton and Cook (1963), the average silver content in wet tissue of Americans is about 0.05 ppm. The body of a 150-lb human, whose tissue content was 0.05 ppm, would contain only 32 mg silver or 3.2 per cent of a 21-year ingestion total. It would appear that very little of the silver ingested from nontherapeutic sources is actually retained in the body.

Excretion of radiosilver ($^{110}AgNO_3$) was faster, and a larger percentage of it was excreted in test animals when it was administered orally than when it was injected either i.p. or i.v. More than 90 percent of the carrier-free silver administered by any of these routes was excreted in the feces with at least 90 percent of the orally ingested silver not being absorbed.

In beagle dogs (average age 5.5 years, 12 to 16 kg) given oral doses of 6 μCi ^{110}Ag as the nitrate, about 10 percent of the dose was absorbed. About 70 percent of the absorbed dose had a biological half-life of about one month. Dogs retained 1 percent of the dose for at least four weeks (Furchner, et al. 1968).

---

*Subject A retained 16 percent of the dietary silver she ingested, but Subject B excreted 2.5 times more silver than he ingested from his diet. (Both A and B excreted about the same amounts of silver in their urine.) Subject B was also in negative balance for copper, barium, and nickel. His medicine intake and occupation were not mentioned nor was the state of his dental restorations.

Female RF mice (eight weeks old, 2 g), given ^{110}Ag as the nitrate i.p., i.v. (tail vein or jugular vein), or orally (12 mice per route) lost half the dose much faster than did the rats of Scott and Hamilton (1950). The rats required 30 days to eliminate 99 percent of the dose, whereas the mice required only 18 days. Almost the entire oral dose (given by stomach tube) was lost by the mice with a biological half-life of 0.125 day. The biological half-life of the remainder was 1.5 days. "The body burden under conditions of chronic oral ingestion would be only about one-fifth of the daily dose" (Furchner, et al. 1966a).

The plots of effective retention versus time of oral doses of ^{110}Ag in 12 mice, 6 rats, 4 monkeys, and 4 dogs showed that within the first day or so, the rate of elimination decreased in the order: rats→dogs→mice→monkeys; but at 5 days, the order was rats→mice→monkeys→dogs; and at 15 to 35 days, the order was mice→rats→monkeys→dogs. The urinary/fecal ratio on day 1 for rats and mice was 0.001; for monkeys, 0.02 (Furchner and Drake, 1968).

When a one-time dose of ^{110m}AgI (1 µCi ^{110m}Ag in 0.5 g AgI) was force-fed to three cottontail rabbits, 99 percent of the dose was excreted within three days, the elimination half-life being 0.48 day. From 8 to 26 percent of the radiosilver entered the cecum (as judged in three rabbits prevented from reingesting their cecal pellets) (Jones and Bailey, 1974).

Four rabbits were fed 0.00042 percent silver, in the dry matter of feed, as silver iodide complexes prepared to simulate cloud-seeding generator products for 30 days. The concentrations of silver in the dry matter of feces and cecal contents were similar (4.2 to 5.2 mg/kg). The silver content of the dry matter of their livers (0.2 mg/kg) was the same as that in four control rabbits fed a normal diet (0.00001 percent silver); thus, absorption was not likely (Jones and Bailey, 1974).

Roy and Bailey (1974) concluded that accumulation of silver in the rumen of any ruminant species upon chronic intake is not likely. The presence of chloride ions, protein, bacteria, and other organic matter in the rumen inhibit the antimicrobial action of silver ions and insure that most of the ingested silver* passes from the rumen in an insoluble form.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The toxicity of silver compounds could be classified as moderate, although large doses of silver compounds may have serious effects (Table 13). For example, ingestion of 10 g silver nitrate is usually fatal. In humans taking large doses of silver nitrate orally, the patient suffers violent abdominal pain, abdominal rigidity, vomiting, and convulsions and appears to be in severe shock. Patients dying after i.v. administration of Collargol® (silver plus silver oxide) showed necrosis and hemorrhages in the bone marrow, liver, and kidney (Hill and Pillsbury, 1939). In the body, silver may be precipitated by protein or chloride ion. Table salt (sodium chloride) is an antidote for silver nitrate poisoning.

*Silver iodide or silver nitrate at levels simulating 0.0001 percent and 0.01 percent, respectively, in the dry feed were inserted with small amount of feed in nylon bags into fistulas in the rumens of goats.

TABLE 13

Acute Toxic Effects of Silver on Humans*

How Administered	Dosage	Survival Time	Observed Effects	Remarks
i.v. Collargol®	36 cc of 12% soln.	3-14 days	Purpura hemorrhagica on the 4th day. Death. Ag chiefly in the reticuloendothelial system.	
i.v. Collargol®	32 cc of 5% soln.	3-14 days	Extensive necrosis and hemorrhage of bone marrow, liver, and kidney.	
i.v. Collargol®	To fill renal pelvis for X-ray study		Death. Severe hemorrhagic diathesis with parenchymatous hemorrhages in the stomach, intestines, and body cavities.	
i.v. Collargol®	10 cc of 2% soln.	5 min.	Cyanosis, coma; death due to pulmonary edema.	No Ag found in lungs.
Intravaginally	2 cc unknown concn. of $AgNO_3$		Death.	Abortion attempt. Death possibly not due to $AgNO_3$.
Oral	8 g $AgNO_3$ in soln.		Vomitus contained AgCl.	Patient recovered.
Oral	2-30 g $AgNO_3$	A few hr. to a few days	Usually death at dosages 10 g.	10 g is usually fatal, but 30 g has been survived.
Oral metallic Ag	50-260 g		Gastric fullness, anorexia, gastric pain, and/or diarrhea.	

*Source: Hill and Pillsbury, 1939.

There is little likelihood of systemic effects in people recovering from toxic doses, but silver may cause degenerative liver changes (Dreisbach, 1963).

The most common noticeable effects of chronic and, less frequently, subacute human exposure to silver or silver compounds are generalized argyria, localized argyria, and argyrosis (argyria of the eye unless stated otherwise). The two most important causes of argyria are medicinal application of silver compounds and occupational exposure. Numerous case histories from Hill and Pillsbury (1939) are summarized in Table 14. Generalized argyria is a slate gray pigmentation of the skin, hair, and internal organs caused by deposition of silver in the tissues. The degree of pigmentation is highest in areas of the skin most exposed to light, but the concentration of silver in the skin from various parts of the body is the same. Silver also accumulates in the blood vessels and connective tissue. Additional manifestations of generalized argyria include: silver coloration of fingernails and conjunctiva and blue halo around the cornea. In localized argyria, only limited areas are pigmented.

Every silver compound in common chemical use has caused generalized argyria. Of 239 recorded cases of generalized therapeutic argyria analyzed by Hill and Pillsbury (1939), 118 were caused by silver nitrate and 28 by Argyrol® (mild silver protein), the second most frequent causative agent. Only 19 were caused by i.v. injection of silver arsphenamine. Of 178 cases, in which the route was

TABLE 14

Argyria

Observed Effect	Ag Compound	Exposure Conditions	Length of Exposure	Time Until Appearance of Argyria	Ag Intake or Total Dose	Ag Excretion	Remarks	Reference
Increased densitries in lung X-rays	Ag particles	Silver polishers	Long periods				Ag impregnation of vascular elastic membranes.	ACGIH, 1971
Localized argyria	Ag particles	Penetration of fine particles						ACGIH, 1971
Generalized argyria	Ag salts	Ingestion or inhalation of Ag salts						ACGIH, 1971
Argyrosis		1-2 mg Ag/m^3 in air during spraying operations in manufacturing Ag varnish and in silvering radio-tech. parts					11 were affected in upper respiratory passages. 9 in conjunctiva or cornea.	ACGIH, 1971
Generalized argyria, possibility of	Ag in air	Breathe 10 m^3 air/day retention of 50% of Ag (assumed)	20 years		5-fold the recommended TLV, 0.05 mg/m^3, would lead to accumulation of 1.2 g Ag.			ACGIH, 1971
Generalized argyria		Medication or industrial exposure			Primarily in Lung and G.I. tract.	Absorbed via feces; only traces in urine.	G.I. tract or by dust inhalation.	Browning, 1961
Generalized argyria						Very slight, over 3 week-long periods.		Browning, 1961
Argyria - no recognizable health disturbances							Possible cause of kidney lesions with consequent dangers of arteriosclerosis and lung damage but not fibrosis.	Browning, 1961
Pulmonary argyria							Often have bronchitis and emphysema, but no cause-effect relationship has been established.	Gafafer, 1964

TABLE 14 (Continued)

Observed Effect	Ag Compound	Exposure Conditions	Length of Exposure	Time Until Appearance of Argyria	Ag Intake or Total Dose	Ag Excretion	Remarks	Reference
Lung pigmentation	Ag and Fe_2O_3	Worked as a silver finisher					Due primarily to Fe, but Ag present	Johnstone and Miller, 1960
Generalized argyria	$AgNO_3$	Administered orally to treat epilepsy and G.I. symptoms	Weeks to 20 years	E.g., 2 years after taking 600 g for 1.2 year	9–1,000 g			Hill and Pillsbury, 1939
Generalized argyria	Protargol®	300-g soln. instilled into urethra daily	2 days	3 days				Hill and Pillsbury, 1939
Generalized argyria	$AgNO_3$, stick	Local application for sore throat and tongue ulcers	0.5–20 years	E.g., 1 year (when used for 3 years)				Hill and Pillsbury, 1939
Generalized argyria	Collargol®	Administered orally to treat pulmonary tuberculosis	E.G., 5 years (260 g Ag)	1 year	50–530 g			Hill and Pillsbury, 1939
Generalized argyria	Ag arsphenamine	i.v.	2–10 years	16 months to 9 years	0.91–7.6 g			Hill and Pillsbury, 1939
Generalized argyria							201 cases from 1700 to 1939	Hill and Pillsbury, 1939
Localized argyria							17 cases from 1700 to 1939	Hill and Pillsbury, 1939
Argyrosis							57 cases from 1700 to 1939	Hill and Pillsbury, 1939
Industrial argyrosis							12 cases from 1700 to 1939	Hill and Pillsbury, 1939
Localized argyria of gums	Dental alloy	During preparation for a dental crown						Burton, 1970
Mottled pigmentation	AgC:CH	Explosion					Caused blue pigmentation	Orentreich and Pearlstein, 1969

other than i.v., 89 were caused by oral intake of silver, chiefly as the nitrate or as colloidal silver plus silver oxide, and another 75 by administration to the nose and throat.

Silver compounds, with the possible exception of silver oxide, are not absorbed through unbroken skin in significant amounts, but absorption occurs through wounds and mucous membranes. Localized argyria of therapeutic origin is relatively rare, usually resulting from topical administration to the conjunctiva, nasal mucosa, tissues of the mouth, or skin ulcers.

Argyrosis involves all eye tissues except the optic nerve. Instillation of 0.25 percent silver nitrate for three weeks and instillation of 3 to 5 percent silver colloidal compounds for 5 to 10 weeks have produced argyrosis (Hill and Pillsbury, 1939).

Colloidal silver compounds have been widely used to treat upper respiratory infections, but the amount of silver absorbed and permanently retained by the respiratory tract has not been determined. The total safe period for nasal instillation of colloidal silver compounds is believed to be 3 to 6 months. Colloidal silver compounds in the nose interfere with normal ciliary activity (Hill and Pillsbury, 1939).

Urethral application of Protargol® for treatment of gonorrhea resulted in argyria after two days, the most sudden onset of argyria reported. Silver nitrate-impregnated compresses applied to abraded skin caused argyria 14 days after the treatment. In only two other cases did argyria result in less than six weeks after treatment (Hill and Pillsbury, 1939).

Generalized argyria as an occupational disease was never common. It occurred almost exclusively among silver nitrate makers and is now disappearing due to improved work conditions. Some workers involved in mirror plating, glass bead silvering, silver Christmas cracker manufacturing, photographic plate manufacturing, silver mining, and packaging silver nitrate have developed argyria as a result of ingestion or inhalation of silver fulminate, nitrate, albuminate, and cyanide (Schwartz, et al. 1947). Bronchitis and emphysema have been described in workers with pulmonary argyria, but a cause-and-effect relationship has not been established (Gafafer, 1964).

Argyrosis occurred in all cases of argyria caused by occupational exposure and was generally more pronounced than therapeutically produced argyrosis. Localized argyria is rare, usually resulting when silver compounds contact broken skin or mucous membranes (Hill and Pillsbury, 1939). It has occurred in workers who handle metallic silver in filing, drilling, polishing, turning, engraving, forging, soldering, or smelting operations. Local argyrosis has occurred in electroplaters, firecracker makers, silver mirror manufacturers, etc. Silver polishers, exposed over long periods, sometimes exhibit increased densities in their lung X-rays due to silver impregnation of the elastic membranes of the pulmonary vessels. Pigmentation occurs slowly in workers who develop localized argyria--50 percent of the workers have been employed 25 years or more. The time of the onset of pigmentation has varied 2 to 38 years (ACGIH, 1971; Hill and Pillsbury, 1939).

In three cases, post-mortem examination showed the distribution of silver in the tissues of persons having argyria resulting from occupational exposure was the same as the distribution of silver in tissues of those having therapeutic argyria (Hill and Pillsbury, 1939).

Several toxic effects, only indirectly attributable to silver, have been reported from use of silver compounds in treatment of burn patients. Most of them occur within a few days of initial treatment and are readily corrected by appropriate treatment; the duration of silver treatments probably seldom extends into the chronic range ($\geq$13 weeks).

Because of the hypotonicity of the 0.5 percent silver nitrate dressings and the tendency to precipitate as silver chloride, electrolyte imbalance may occur in a few hours (Wood, 1965). Electrolytic disturbances are also occasionally found in patients treated with silver sulfadiazine (Burke, 1973). For that reason, the electrolytes in the patient's blood are closely monitored and supplemented when necessary. Severe electrolyte depletion is especially common in children during prolonged use of 0.5 percent silver nitrate in burn therapy (Bondoc, et al. 1966).

Methemoglobinemia is sometimes induced in patients treated with silver nitrate because of the reduction of the nitrate to nitrite by bacteria in the patient's skin, not because of the presence of nitrite in the original solution. Cultures of endobacteria from a burn patient exhibiting methemoglobinemia readily reduced nitrites (Strauch, et al. 1969a). An absorptive surface, such as a granulating wound or damaged skin, is also needed (Strauch, et al. 1969b). Strauch, et al. (1969a) recommended that discontinuation of silver nitrate therapy in patients with up to 30 percent methemoglobinemia would return patients' hemoglobin levels to normal within 24 to 72 hours. However, if the level is greater than 30 percent the patient must be actively treated with methylene blue.

Silver sulfadiazine (Silvadene®, Marion Laboratories, Kansas City, Missouri) is used increasingly to prevent infections from _Pseudomonas aeruginosa_ and other bacteria in treatment of burn patients. It is preferred to silver nitrate treatments because it does not deplete the body of sodium, chloride, or potassium.

Henderson (1975) stated that the finding of leukopenia in burn patients being treated with silver sulfadiazine (Silvadene® cream) was not due to the treatment but to the thermal injury itself. Daniels, et al. (1975, cited by Henderson, 1975) had found that depressed white blood cell count and suppressed immune response were often seen in burn patients. Gayle and Haynes (1976, cited by Kiker, et al. 1977) had seen marked leukopenia in burn patients treated with silver sulfadiazine. Kiker, et al. (1977) performed a double-blind study with a nonantimicrobial placebo in the control group to determine if the leukopenia was due to the silver sulfadiazine therapy or to the thermal injury. Thus, 60 juvenile patients with a mean area burned of 48 percent of the body surface and treated with the placebo showed a white blood cell count of $11.8 \pm 2.5 \times 10^3/mm^3$. The 69 juvenile patients (52 percent mean area burn) receiving silver sulfadiazine treatment had a white blood cell count of $12.2 \pm 2.1 \times 10^3/mm^3$. There was no significant difference in the white blood cell count of the two groups ($p > 0.05$); six placebo-treated patients and five silver sulfadiazine-treated patients developed leukopenia ($WBC < 5,000/mm^3$). In a second similar study with 175 patients receiving silver sulfadiazine, 5.7 percent developed leukopenia. In all cases, the leukopenia resolved itself without discontinuing the therapy.

Valente and Axelrod (1978) maintain that the leukopenia observed during silver sulfadiazine therapy is due to the sulfadiazine portion of the drug (most of the silver remains at the wound bound to tissue and bacterial proteins and DNA), not the injury. They aspirated the bone marrow of a burn patient exhibiting leukopenia on two occasions within 48 hours of treatment with Silvadene® and noted cell maturation arrest.

Renal injury, sometimes fatal, and sensitivity following sulfonamide therapy is well-known. Owens, et al. (1974) reported the first case of nephrotic syndrome apparently due to topical application of silver sulfadiazine. The electron-dense deposits seen in the glomerular basement membrane suggested an immune-complex mechanism. No attempt was made to identify the deposits as silver since precipitation of crystals has been observed during other sulfonamide-induced renal damage.

Fox (1973), when asked to discuss side effects that had occurred in the five years of use of silver sulfadiazine cream in burn treatment, remarked that two cases of apparent skin sensitivity had come to his attention.

Aside from burn therapy and use of medications applied to mucous membranes, silver metal has been used in surgery. Silver points have been used for years to induce apical bone healing in dental surgery. Because of the recognized cytotoxicity of silver corrosion products, Weissman (1975) recommended that titanium points be substituted for silver.

Argyrosis of the cornea in workers who handle silver nitrate may be accompanied by turbidity of the anterior lens capsule and a disturbance of dark adaptation. Deposition of silver in the eye does not usually result in loss of vision (Browning, 1961).

Two silver nitrate workers afflicted with argyrosis of the lung showed mild chronic bronchitis with silver impregnation in the walls of the middle and upper region of the nasal mucosa. In a more severe case, the bronchial mucous membrane also showed basal membrane deposits and some squamous metaplasia. There was less evidence of phagocytosis than in the nasal mucosa and no hazard of fibrosis. Pigmentation was comparable with that of anthracosis and siderosis (Browning, 1961).

Grant, et al. (1975) analyzed by atomic absorption spectrophotometry the lung tissues of 11 mummified subjects from northern Peru believed to have been involved in hard-rock silver mining and/or ore refining in the period 1500 to 1600 A.D. High levels of mercury were found in most tissues, but there was no statistical correlation between the concentrations of mercury or lead and lung disease. A moderate correlation between lung disease and silver was found.

Marks (1966) reported the case of a 33-year-old woman, a radiographer for 10 years, who exhibited contact dermatitis under her contaminated watch strap. Patch tests showed sensitivity to the thiosulfate complex of silver iodide, fixing fluid which had contacted silver (but not unused fixing fluid), and 1 percent silver nitrate. The sensitivity was assumed, therefore, to be due to ionic silver. Marks had found only one case in the literature of contact dermatitis due to silver. Gaul and Underwood (1948, cited by Marks, 1966) reported a dermatitis in a 27-year-old man who had sensitized himself by using a silver nitrate solution on his feet. In sensitivity tests, he reacted to old 10 percent silver nitrate solution (but curiously not to fresh solution), silver foil, and silver proteinate. Since lists of allergens for patch tests sometimes included 5 or 10 percent silver nitrate solutions, Marks suggested that allergic contact dermatitis was more prevalent when silver nitrate topical treatments were more common.

Zech, et al. (1973) attributed a nephrotic syndrome in an obese, argyric 73-year-old man to silver deposits in the kidney. The man had used a silver-containing mouthwash or gargle for 10 years (1955 to 1965), presumably corresponding to the absorption of a total amount of 88 g of silver. The patient showed respiratory insufficiency and a nephrotic syndrome with proteinuria, elevated a_2 macroglobulins, and glomerular (but not tubular) involvement. Silver deposits were found in the glomerular basement membrane.

The toxicity of silver to species other than mammals and birds will not be discussed because of its inapplicability to human toxic effects.

Acute effects from silver in mammals are usually associated with i.v. administration. For example, silver nitrate has been used frequently since 1932 to produce acute pulmonary edema for study. Dogs injected with 0.5 ml of 10 percent $AgNO_3$/kg ($\sim$32 mg Ag/kg) into the left ventricular wall or the pulmonary artery developed the edema, myocardial ischemia and lesion, hypertension, and swelling and necrosis of wall and endocardium. Genesis of pulmonary hypertension and edema by silver nitrate depends on its entering the pulmonary circuit, and the mechanism involved is probably stimulation of vagal terminations (Sales and Duarte, 1960). Intravenous injections of silver nitrate in dogs produced hemodynamic disturbances resulting in pulmonary edema, with circulatory hypoxia causing death (Mazhbich, 1961).

Hill and Pillsbury (1939) reviewed the early literature on the toxic effects seen in animals given various medicinal forms of silver. When inorganic compounds were given i.v., the effects were chiefly on the central nervous system. The animals receiving lethal doses showed weakness, rigidity, and contractures in the legs, loss of voluntary movements, and interference with cardiac blood supply. LD_{50} data apparently were not calculated.

The oral LD_{50} for silver sulfadiazine in CF_1 mice has not been determined, but the LD_{90-100} was $>$ 1,050 mg (Wysor, 1975b and 1977).

The i.p. LD_{50} (30 days) for Ag^+ as the nitrate in male Swiss albino mice (21 ± 2 g) is 13.9 mg/kg, indicating that Ag^+ is 345 times more toxic than Na^+ (as the chloride) (Bienvenu, et al. 1963).

Rabbits receiving 20 injections on their depilated backs of a silver salt dissolved in distilled water (0.01 M) showed papules which had a minimum diameter of 5 mm within 24 hours. Of the Group I metals tested, only silver and gold produced skin reactions (gold at 0.1 M concentration) (Muroma, 1961).

Some of the toxic effects of Ag^+ and other heavy metal ions may be due to their alteration of cyclic adenosine monophosphate (AMP) metabolism, which would be expected based on *in vitro* experiments by Nathanson and Bloom (1976): an 8 μM solution of silver nitrate caused 50 percent inhibition of adenylate cyclase in a rat cerebellar homogenate, and a 30 μM solution caused 58 percent inhibition of phosphodiesterase, in a 0.1 μM solution of cyclic AMP.

Most of the subacute dosing experiments with silver compounds are summarized in Table 15. Except for the corrosive nature of low doses of silver nitrate, most of the other compounds tested were reasonably tolerated by the animals in periods up to 71 days.

Yoshikawa (1970) reported that mice given pretreatments with certain heavy metals, including silver, lead, cadmium, and mercury, developed a tolerance to a lethal dose* of the metal as shown by

---

*The pretreatment dose was 10 percent of the challenge dose. The challenge dose was "about 70 to 80 percent lethal doses," presumably the LD_{70-80}.

TABLE 15

Acute Effects of Silver on Terrestrial Animals

Animal	How Administered	Dosage	Survival Time	Observed Effects	Remarks	References
Rats	s.c. injection $AgNO_3$	7 mg/kg body wt.		Affected testis histology and spermatogenesis. Peripheral tubules affected and some central tubules completely degenerated after 18 hr. Some tubules recover. Duct system seldom fully recovers.	Marked deformation of tubules at head of epididymis Epithelial cells appeared swollen. Spermatogenesis active.	Hoey, 1966
Rats	s.c.	0.35 or 0.7 mg/100 g body wt.		Decreased threshold of electrical stimulation of epileptiform convulsions.	No clinical symptoms of intoxication.	Fedotov, et al. 1968
Rabbits	i.v. Cryptargol®	1-3 cc soln. contg. 0.1 g Ag/cc	4-48 hr.	Congestion of kidneys, tubular swelling, and/or glomerular necrosis.		Hill and Pillsbury, 1939
Rabbits	i.p. $AgNO_3$	20 mg/kg in neutral soln.	2 hr.	Death in coma. Degenerative aspects and Ag granules in liver parcenchyma and kidney tubules.	No abnormalities in heart, lungs, brain, or adrenals.	LaTorraca, 1962
Guinea pig	2 ml i.p. $AgNO_3$	0.239 M $AgNO_3$	1-7 days	Death.		Wahlberg, 1965
Dogs	i.v. Collargol®	200-300 mg		Well tolerated.		Shouse and Whipple, 1931
Dogs	i.v. Collargolum® (1% emulsion of Ag)	500 mg	12 hr.	Pulmonary edema, anorexia, profound anemia, active hyperplastic bone marrow.	Also had weight loss and weakness.	Browning, 1961
Dogs	i.v. Collargol®	500 mg	24 hr.	Death, hemolysis, lung edema.	A dog given 2,600 mg Collargol over 4 months in doses of 20-600 mg died after the last injection of 600 mg.	Shouse and Whipple, 1931
Dogs	i.v. Ag albuminate	0.03 g	0.5 hr.	Death.		Hill and Pillsbury, 1939

TABLE 15 (Continued)

Animal	How Administered	Dosage	Survival Time	Observed Effects	Remarks	References
Dogs	i.v. $Ag_2S_2O_3$	0.2 g in 60 cc H_2P		Death in convulsive seizures, pulmonary edema.	At lower dosages: anesthesia and paralysis of hind legs followed by increased bronchial secretion and asphyxial death.	Hill and Pillsbury, 1939
Dogs	i.v. $AgNO_3$			Death due to mechanical asphyxia.		Hill and Pillsbury, 1939
Dogs	i.v. $AgNO_3$	32 mg		Death.		Hill and Pillsbury, 1939
Dogs	i.v. Argyrol®	3 mg/kg	18 hr.	Death despite regular respiration while in coma.		Hill and Pillsbury, 1939
Dogs	i.v. Argyrol®	4-5 mg/kg		Also had edema of lungs and intestinal hemorrhages.		Hill and Pillsbury, 1939
Dogs	i.v. Colloidal Ag	100 mg		Hemolysis.		Hill and Pillsbury, 1939
Dogs	$AgNO_3$ placed directly in stomach	2.3-2.6 g	A few days if vomiting is impeded.	Death if vomiting prevented.		Hill and Pillsbury, 1939
Horses	i.v. (?)	$AgNO_3$		Death, hemorrhage and thrombi of heart and kidneys.		Hill and Pillsbury, 1939

TABLE 15 (Continued)

Animal	How Administered	Dosage	Survival Time	Observed Effects	Remarks	References
Rabbits	i.v. Cryptargol® daily	0.6 cc soln. contg. 0.1 g Ag/cc		No albumin or casts in urine.	Administered for 71 days.	Hill and Pillsbury, 1939
Rabbits	i.v. Ag arsphenamine (14.5% Ag)	66.7 mg/kg for 47-70 days		More Ag retained by animals losing weight. Most showed a gradual increase in hemoglobin and red blood cells. No toxic effects or discoloration.	Minimum dosage 277 mg in 47 days. Maximum dosage 2,363 mg in 70 days.	Hill and Pillsbury, 1939
Dogs	i.v. Collargol®	1,300-1,500 mg over 3-7 days		Tolerated.		Shouse and Whipple, 1931
CF-1 Mice	Oral or s.c. silver sulfadiazine	1,050 mg/kg/day for 30 days		Cured mice of their infection by Plasmodium berghei within 5 days even after a splenectomy. Also effective against systemic infection by Pseudomonas aeruginosa. The mice did not show any histological pathology, weight loss, or abnormal behavior. There was a local granulomatous lesion at the s.c. injection site.		Wysor, 1977 Wysor, 1975b
Rats	s.c. Ag-contg. substance not identified	3,5-7 mg/kg for 14 days		Decreased threshold of epileptogenic effect of electrical stimulation.	No clinical symptoms of intoxication.	Fedotov, et al. 1968

fewer deaths in the pretreated mice compared with mice that were not pretreated. Thus, when 10 male ICR mice were given an i.p. dose of 3.5 mg Ag/kg as silver nitrate before the challenge dose of 35 mg/kg 24 hours later, only three of the pretreated mice died within seven days, compared with eight of the nonpretreated mice.

Dymond, et al. (1970) implanted wires of several metals and alloys including pure silver into the brains of cats for two months. Silver produced a toxic effect as shown by a very large scar with a large component of glial elements. The author cited other reports wherein silver or silver/silver chloride was toxic as a brain implant. (Other studies wherein implants were maintained for longer than two months are described under chronic studies).

Olcott (1950) gave rats either silver nitrate or thiosulfate in 1:1,000 concentration (635 mg Ag/l if $AgNO_3$ and 660 mg Ag/l if $Ag_2S_2O_3$) in their drinking water for up to 30 months. The finding of hypertrophy of the left ventricle in a statistically significant number of rats was presumed to indicate that the rats had developed vascular hypertension, possibly due to thickening of the basement membranes of the renal glomeruli.

Olcott (1948) had given rats 1:1,000 concentration of silver nitrate or thiosulfate in their drinking water for their lifetime, beginning shortly after weaning, without observing any shortening of the lifespan. Skin pigmentation was not observed, but the internal organs (the pancreas was especially dark) and the eyes were darkened by silver deposits. Absorption was apparently via the small intestine based on the large amount of silver found in its villi. The deposition of silver in internal organs and tissues usually resembled that seen in humans with argyria.

The following chronic studies are arranged in order of the lowest chronic dose administered.

Albino rats receiving doses of 0.00025 and 0.0025 mg electrolytic silver per kg body weight in their drinking water for 11 months did not show any changes in conditioned-reflex activity. The dose 0.0025 mg/kg corresponds to 0.05 mg/l in the water (Barkov and El'piner, 1968). Doses of 0.025 (0.5 mg/l) and 0.25 mg Ag^+/kg in rats did affect the conditioned reflex activity. These doses during 11 months also lowered the immunological activity of rabbits as judged by increasing phagocytosis by blood leukocytes. Pathological changes were noted in vascular, nerve, brain, and spinal cord tissues (Barkov and El'piner, 1968).

None of the doses induced changes in the hemoglobin content, number of erythrocytes, the leukocyte count, the protein-forming function of the liver, and the content of thiol groups in the blood (Barkov and El'piner, 1968).

Rats receiving 0.05 mg Ag^+/l in their drinking water for five months showed no effect on gastric secretion, blood serum enzymes, or morphology of the stomach, intestine, liver, and kidney. Pathomorphological changes in stomach, small intestine, and liver were noted, however, in rats receiving 20 mg Ag^+/l. Blood serum asparagine transaminase and alanine transaminase were increased >2 and 2.4 times over the level in the control group, respectively, and growth was depressed 36 percent at the higher concentration (Maslenko, 1976).

Pak and Petina (1973) gave 94 white rats of both sexes 0.1, 20, and 50 mg Ag^+/l for 4 and/or 6 months while the 20 controls drank the Moscow water supply. When Ag^+ was supplied as silver nitrate, after four months there was a small decrease in the -SH groups in the blood serum (51.2 versus 57.0 μM in the controls) at 50 mg/l. Anodically produced silver of the same concentration did not produce this effect. But after six months, both forms of Ag^+ at 20 mg/l depleted the -SH groups: ionic silver, 31.2 μM; $AgNO_3$, 35.3 μM; and controls, 50.0 μM. At four months, the 0.1 mg/l concentration had actually increased the concentration of -SH groups in blood serum to 63.0 to 64.0 μM.

Kul'skii, et al. (1973) reported that 0.100 to 0.200 mg Ag^+/l in the drinking water of test animals did not affect the antimicrobial and antiviral immunity formation in the animals (Savluk, 1973). There was also no effect on the ratio of the blood-forming elements (Savluk and Moroz, 1973), the protein content, the functional state of the spleen, or conditioned-reflex development (Kharchenko and Stepanenko, 1972; and Zapadnyuk, et al. 1973).

The function of the reticuloendothelial system in the manufacture of specific protective factors in rats receiving 0.2 and 20 mg Ag^+/l in their drinking water for eight months was not altered, but albino mice receiving the higher dose showed reduced absorptive capacity of the reticuloendothelial system (Savluk, 1973).

Kharchenko and Stepanenko (1972) (see also Kul'skii, et al. 1972) found no change in conditioned-reflex activity in male (8 or 15 or 16 per group) albino rats given drinking water with 0.2 to 0.5 mg Ag^+/l for six months and insignificant changes in rats given

2 mg Ag^+/l. However, at 5 to 20 mg/l, intoxication was observed beginning the 25th to 27th day. At that time, there were no conditioned reflex changes. A dose of 20 mg/l had inhibited the intensity and prolonged the latent period of the cortical response to stimuli by the end of the second month. The latent period of the conditioned reflex was 2.5 times that of the controls. On prolonged ingestion, there occurred an increase of excitability, an increase in the number of intersignal reactions, differentiation disinhibition, and disturbances in mobility and equilibration of main nervous processes. After 5 to 6 months at 20 mg/l, the inhibition of the positive conditioned reflexes again occurred, with increasing intensity.

Male albino rats (five), drinking water containing 20 mg Ag^+/l for eight months, showed a significant decrease in the escape rate from an aqueous labyrinth as compared to controls. In a 12-month study the repressing effect on the rate of the first swim to escape from an aqueous maze was an average 22 percent greater in rats that had drunk water containing 500 µg/l and 47 percent in those drinking 2,000 µg/l (Zapadnyuk, et al. 1973). The repressing effect on the rate was less at 2 mg/l and even less at 0.5 mg/l, but those rats receiving 0.2 mg Ag^+/l (0.01 mg Ag/kg body weight) showed no difference (Zapadnyuk, et al. 1973).

Savluk and Moroz (1973) studied changes in the blood of albino rats (240 total) receiving electrolytically produced silver ions for three months in their drinking water at 0.2 mg Ag^+/l (0.03 mg/kg/day) and 20 mg Ag^+/l (3.0 mg/kg). No changes were noted in the hemoglobin; number, color, and form of the erythrocytes; the color index of the blood; and the precipitation reaction of the erythrocytes. The increase in the number of leukocytes in the test rats was statistically insignificant. Upon electrophoretic analysis, there was no significant difference in the protein fraction ratio of the blood of the rats receiving 0.2 mg/l from that of the controls. There seemed to be an increase in gamma and betaglobulin fractions. At 20 mg Ag^+/l, there still was no statistically significant difference in the ratio of protein fractions in comparison with that of the controls; yet the slight increase in the globulin fractions was accompanied by a lowering of the amount of albumins and total protein in the blood.

A slight change in protein metabolism shown by changes in the amount of proteins in each fraction in the serum reverted to normal by two months after the end of silver intake.

The 0.2 mg/l animals showed no change in liver function, but the higher concentration lowered the weight of both the liver and whole animal. It was concluded neither level was toxic to the liver.

The higher concentration increased the amounts of almost all 16 free amino acids determined in the blood serum (Savluk and Moroz, 1973).

The changes in brain nucleic acids of rats after chronic intake of silver as determined by Kharchenko, et al. (1973b) are shown in Table 16. Male albino rats (three), drinking water containing 0.5 mg Ag^+/l for six months from the time they were three months old, showed increased body weight compared with the controls, lowered nucleic acid content in the brain, and increased

TABLE 16

Quantitative Changes in Nucleic Acids in the Brain of Rats*

Concentration of Silver, mg/l	Weight of Animal, g	Weight of Brain, g	Concentration of Nucleic Acids in Brain, mg %		Contents of Nucleic Acids in Brain, mg		Number of Nuclei in Brain, 10^6	Weight of Brain/ Nucleus	Content of DNA/ 100 mg Dry Weight of Brain	Ratio of the RNA/DNA Content in Brain
			DNA	RNA	DNA	RNA				
After Intoxication with Silver for 6 Months										
Control	249 ± 20	1.93 ± 0.07	13.9 ± 1.6	12.7 ± 0.8	2.75 ± 0.36	2.57 ± 0.2	444 ± 59	4.8 ± 0.8	0.141 ± 0.016	1.0 ± 0.19
0.5	274 ± 23	1.92 ± 0.05	12.0 ± 0.7	8.5 ± 1.8	2.33 ± 0.03	1.73 ± 0.38	376 ± 13	5.1 ± 0.3	0.119 ± 0.021	0.75 ± 0.18
P	0.556	0.091	0.683	0.920	0.695	0.90	0.695	0.39	0.561	0.478
20	278 ± 57	1.95 ± 0.14	19.3 ± 0.5	16.2 ± 1.1	3.79 ± 0.26	3.32 ± 0.29	612 ± 30	3.2 ± 0.1	0.194 ± 0.007	0.88 ± 0.08
P	0.423	0.099	0.95	0.95	0.941	0.922	0.95	0.906	0.95	0.512
After Intoxication With Silver for 12 Months										
Control	313 ± 42	1.9 ± 0.12	15.7 ± 0.9	16.9 ± 2	3 ± 0.2	3.4 ± 0.3	487 ± 31	3.9 ± 0.13	0.159 ± 0.009	1.12 ± 0.08
0.5	379 ± 28	2.1 ± 0.1	15.5 ± 0.8	17.7 ± 1.2	3.3 ± 0.1	4 ± 0.1	589 ± 13	4 ± 0.2	0.156 ± 0.008	1.19 ± 0.02
P	0.720	0.806	0.124	0.264	0.785	0.849	0.785	0.073	0.181	0.529
2	326 ± 44	2.1 ± 0.08	18.2 ± 0.49	18.8 ± 1.9	3.9 ± 0.1	4.1 ± 0.5	625 ± 13	3.4 ± 0.1	0.184 ± 0.006	1 ± 0.1
P	0.216	0.766	0.892	0.466	0.95	0.720	0.95	0.893	0.897	0.264
20	338 ± 84	1.9 ± 0.1	12 ± 1.2	8 ± 1.2	2.3 ± 0.3	1.6 ± 0.1	374 ± 47	5.2 ± 0.6	0.121 ± 0.011	0.7 ± 0.1
P	0.195	0.444	0.921	0.95	0.859	0.99	0.862	0.859	0.924	0.95

*Source: Kharchenko, et al. 1973b

weight of brain per cell nucleus (thus, hypertrophy of the cells). After 12 months on this regime, both brain and body weights of three rats were higher than those of the controls, the content of brain nucleic acids was higher, the weight of brain per nucleus was about the same as those of the controls, and the RNA/DNA ratio was higher. These effects were generally more pronounced, but in the same direction in rats (three) receiving 2 mg Ag^+/l 12 months. However, the weight of brain per nucleus and the RNA/DNA ratio was lowered (that is, DNA content had increased more than the increase in RNA) (Kharchenko, et al. 1973a,b).

After 20 mg Ag^+/l for six months, all of the indices were increased except that the weight of the brain per nucleus and the RNA/DNA ratio was reduced. After 12 months on this concentration, all indices were reduced compared with those of the controls except for increased body weight, identical brain weight (which would indicate dystrophy since brain weight was higher at six months), and increased weight of brain per nucleus (Kharchenko, et al. 1973b). Significant changes ($p = 0.95$) were seen in rats drinking 500 μg of silver/l for six months (liver weight 8.7 ± 0.3 g versus 7 ± 0.6 g in the controls and RNA content 61.8 ± 4.9 mg percent versus 77.9 ± 4.7 mg percent in the controls). The DNA content of the liver was significantly elevated (39.4 ± 2.7 mg versus 25.4 ± 4.1 mg in the controls) in the rats drinking the silver concentration for 12 months.

Apparently, as the animals aged and silver accumulated, the presumed protective action of increased content of brain nucleic acids was weakened. An increase in the number of nuclei in the brain apparently was also a protective action. Lowering the RNA/DNA ratio reflected the lowering of metabolic reactions in the brain tissues. In the controls, the intensity of nucleic acid metabolism in the intact animal was somewhat increased with growth (Kharchenko, et al. 1973b). An increase in brain DNA may well indicate tissue damage.

Klein (1978) stated that Just and Szniolis (1936) had observed immunological changes in test animals and had concluded that silver might be harmful to humans in this regard. There is no indication in the paper cited of immunological changes. For 100 days, rats ingested up to 1 mg Ag/l in their drinking water. At concentrations below 0.4 mg/l, the rats appeared in good health, and dissection did not reveal any apparent pathological changes. At 0.4 mg/l, small hemorrhages were detected in the kidney; and there was blood pigment accumulated in some glomeruli, larger vessels, and walls of the caniculi in which hemorrhages had occurred. At 0.7 mg/l, there were large amounts of blood pigment in fresh and old tissue extravasations in the liver; and the changes in the kidney were more marked. At 1 mg/l, pigment was finally observed in the spleen and the changes in the liver and kidney were more pronounced.

At a much higher level of silver--60 mg/kg as silver nitrate or Targesin® (equivalent to 1,200 mg/l if given in drinking water to rats) for "several months", silver nitrate-fed animals showed degenerative kidney changes; the Targesin-fed rats did not (Enders and Moench, 1956).

Bates, et al. (1948, cited by Chusid and Kopeloff, 1962) had found that silver implants in the brain resulted in formation of a surrounding fibrous capsule, necrosis, and infiltration of the cortex and meninges. Fischer, et al. (1957, cited by Chusid and Kopeloff, 1962) had warned that silver or copper wires were unsuitable for use in human depth electroencephalography since they had observed damage and necrosis around such wires in cat brains. Chusid and Kopeloff (1962) inserted a spheroid pellet (3-5 mm diameter) of silver into the brain of one monkey which survived 21 months. The monkey showed spike and slow changes in the electroencephalogram and exhibited a brain lesion classified as a meningocerebral cicatrix in contrast to a necrotizing foreign body reaction, produced by such elements as antimony, cadmium, copper, mercury, and nickel.

To summarize chronic drinking water experiments: rats given 0.05 mg/l silver in their drinking water for 11 months showed no changes in conditioned-reflex activity and for five months, no effect on gastric secretion, blood serum enzymes, liver, or kidney. A concentration of 0.1 mg/l or 0.2 mg/l also appeared to have no effects; but at $\geq$ 0.4 mg/l, hemorrhages were observed in the kidneys. At 0.5 mg/liter for 11 months, conditioned reflex activity and immunological resistance were lowered, and brain nucleic acid content was increased. A concentration of 2 mg/l caused similar effects. By 20 mg/l, numerous physiological changes, including growth depression, were evident. Thus, concentrations of silver ions in drinking water up to 0.2 mg/l (the maximum allowed by Swiss authorities for 38 years) caused no deleterious effects within time periods up to 11 months. Ill effects appeared at 0.4 mg/l, and by 0.5 mg/l, conditioned-reflex activity and immunological activity were reduced.

Synergism and/or Antagonism

Silver exhibits antagonism to selenium, vitamin E, and copper, inducing deficiency symptoms in animals fed adequate diets or aggravating deficiency symptoms when the animals' diet lacks one or more of the nutrients. The effects have been described in dogs, sheep, pigs, rats, chicks, turkey poults, and ducklings.

Shaver and Mason (1951) first noted the toxicity of silver to vitamin E-deficient rats. On 1,500 mg/l silver as the nitrate in their drinking water, the animals developed muscular dystrophy, liver necrosis, and increased mortality. All 23 rats on the low-E diet died within 18 to 40 days except for one survivor for seven months. Diplock, et al. (1967) and Grasso, et al. (1969) found the liver necrosis in rats induced by silver was indistinguishable from that arising in animals that were deficient in vitamin E and/or selenium. Grasso, et al. (1969) also noted necrosis in the brain followed by necrosis of the nuclei, endoplasmic reticulum, and mitochondria. Bunyan, et al. (1968) reported that 3 mg/kg cyanocobalamin in the diet prevented liver necrosis at 0.0130 percent silver in the drinking water or diet.

A silver-induced increase in the selenium content of the mitochondrial fractions of the liver of vitamin E-deficient rats was noted by Diplock, et al. (1971). Grasso, et al. (1969) had observed proliferation of lysosomes in the livers of silver-treated rats deficient in vitamin E. Diplock, et al. (1971) speculated that Ag_2Se accumulation in the lysosomes of the liver mitochondrial may explain the increased selenium retention in the mitochondria fraction in silver-treated rats, although the total amount of selenium in the liver was lowered. They further speculated that perhaps an insoluble silver salt of selenium is formed in the intestine to reduce its absorbability and, therefore, reduce its absolute amount in the liver. Silver-treated rats exhibited greater fecal excretion of ^{75}Se from the diet.

Rats fed diets containing 0.00005 percent selenium and 76 or 751 mg/l silver in their drinking water for 52 days showed liver glutathione peroxidase levels 30 percent and 4 percent, respectively, of the concentration in control rats given the vitamin E-deficient diet with 0.00005 percent selenium as sodium selenite but no silver. The casein-based diet itself contained 0.000002 percent selenium. However, the selenium dietary supplement did improve the growth and survival of rats given 751 mg/l silver (but increased the silver content of liver and kidney) and entirely prevented the growth depression seen in rats given 76 mg/l silver. The silver metabolism was apparently altered because higher silver concentrations were found in the liver. When the diets were made adequate in vitamin E (100 IU/kg), as well as selenium, the glutathione peroxidase levels in liver, erythrocytes, and kidney of rats given 751 mg/l silver in water were 5 percent, 37 percent, and 38 percent, respectively, of those of control rats (Wagner, et al. 1975, and Swanson, et al. 1974).

Whanger (1976b) found that vanadium and zinc apparently promote the liver necrosis seen in rats deficient in selenium and vitamin E, but not to the degree that silver does. The effect of feeding rats nonsupplemented torula yeast diets containing 0.08 percent silver as the acetate was overcome by 40 times (0.004 percent) the required selenium level or by the accepted level of vitamin E (0.006 percent). Whanger (1976b) speculated that vitamin E is more critically involved in counteracting silver than selenium. Both mercury and silver decreased selenium absorption and tissue content, but mercury did not affect the deficiency-caused liver necrosis.

In addition to antagonism to selenium and vitamin E, an isolated report (Dodds, et al. 1937) stated that silver reduced the antidiuretic activity of pituitary extract in rats given 2 μg of the extract plus 0.2 ml of a 5 percent solution of silver lactate per 200 g body weight.

Whanger, et al. (1976a) found that feeding ewes low-selenium diets with 0.005 percent silver as the acetate did not significantly affect the incidence of white muscle disease (a selenium-deficiency syndrome) in their lambs but significantly altered the concentrations of the enzymes glutamic-oxaloacetic transaminase (GOT), creatine phosphokinase (CPK), and lactic dehydrogenase (LDH) in the plasma of the lambs. The relative amounts of plasma GOT for low-selenium, low-selenium plus silver, and low-selenium plus selenium diets were 190:616:44; of CPK, 335:216:32; and LDH, 930:2,694:387. Silver gave higher LDH and GOT concentrations than did arsenic or cobalt.

Higher dietary concentrations of silver were required to produce selenium-vitamin E deficiency in pigs fed an adquate diet. Anorexia, diarrhea, and growth depression appeared in four weanling swine fed a diet adequate in selenium and vitamin E but containing 0.5 percent silver acetate for four weeks. Three of the four pigs died (at 21, 23, or 28 days of the experiment); all had necrotic hepatic lesions; and one had the skeletal muscle and cardiac lesions of selenium-vitamin E deficiency. Pulmonary edema and excessive fluid in the peritoneal, pleural, and pericardial cavities were present. Four pigs fed only 0.2 percent silver acetate for 40 days did not develop any pathological or clinical signs of the deficiency, but the selenium content of the liver was significantly increased (average 0.61 mg/kg wet weight). The lesions and mortality were prevented in two pigs by adding 100 IU/kg α-tocopherol, but selenite was ineffective in two other pigs (Van Vleet, 1976).

McDowell, et al. (1978) found that silver supplementation of 0.02 percent to the low selenium-vitamin E diet* of eight pigs for eight weeks aggravated deficiency symptoms, lowered the selenium concentration of the blood, and increased the selenium concentration in the liver. The pigs reduced their feed intake when it contained silver. The skeletal muscle and cardiac myopathies and the hepatic necrosis were generally more severe in pigs given silver than in those given arsenic or sulfur. The extent of muscular lesions was indicated in silver-treated pigs by the high serum glutamic-oxaloacetic transaminase. The ornithine carbamyl transferase concentration was higher in the pigs treated by silver than with any other agent.

---

*The pigs had been on the deficient diet for 4 weeks before introduction of the silver.

Dam, et al. (1958, cited by Jensen, et al. 1974) found that feeding chicks a diet with 0.002 percent (20 mg/kg diet) silver as the acetate promoted exudative diathesis.

Ganther, et al. (1973) reported that silver at 100 mg/l in the drinking water of chicks promoted the liver necrosis characteristic of vitamin E and selenium deficiency.

Silver acetate at 1,500 mg/l in the drinking water of vitamin E-deficient chicks promoted exudative diathesis. Silver was also found to be a pro-hemorrhagic factor (Bunyan, et al. 1968).

Hill and Matrone (1970) (see also Hill, et al. 1964) found that silver concentration of 0.01 percent (100 mg/kg) in the diet of chicks reduced growth when the diet was deficient in copper. The mortality in the initial 20 chicks was 25 percent after four weeks on a copper-adequate diet compared with 60 percent on a copper-deficient diet. The hemoglobin content of the blood and the elastin content of the aorta was reduced in chicks given a diet with a concentration as low as 0.001 percent (10 mg/kg).

Peterson and Jensen (1975a) obtained results in chicks similar to those described below in turkey poults. Feeding chicks a diet containing 0.09 percent (900 mg/kg) silver as the nitrate for four weeks depressed growth, enlarged the heart, and increased mortality. The growth depression was not completely corrected by a concentration of 0.005 percent (50 mg/kg) copper in the diet, but the cardiac enlargement and mortality were prevented. The 0.09 percent silver in the diet reduced copper concentrations from those of the controls in blood, liver, spleen, and brain, but did not significantly affect copper concentrations in the kidney or excreta. (The latter was only a 1-day sample and may not have been representative.) However, supplementation of the diet with 0.005 percent copper, along with the 0.09 percent silver, brought copper levels to those of the controls in blood, liver (but not fat-free liver), and spleen. Again, the copper content in the kidney was normal, but the concentration in the brain was significantly lower, and that in the excreta was more than twice as high. Possibly, copper loss through the kidneys was being promoted by silver. Silver obviously reduced tissue uptake of copper, but the experiments did not explain whether this was due to interference with copper metabolism or with copper absorption.

When Peterson and Jensen (1975b) performed similar 4-week experiments with chicks fed a 0.09 percent silver diet marginal in vitamin E and selenium, the mortality was mostly due to exudative diathesis. The growth depression and mortality were prevented by including 0.0001 percent (1 mg/kg) selenium or 100 IU vitamin E per kg to the diet. When the silver-containing diet was supplemented only by 0.15 percent cystine, there were signs of exudative diathesis in 58 percent of the chicks after 15 days and 90 percent mortality after 28 days (49 percent and 83 percent, respectively, without added cystine in the diet). Vitamin E was more effective than selenium in reducing the mortality of the cystine-and-silver-fed chicks.

Chicks fed an otherwise normal diet containing 0.0005 percent selenium showed a slower growth rate, and chicks given 0.004 percent selenium for two weeks had increased mortality. Either 0.1 percent silver in the diet as the nitrate or copper as the sulfate improved the growth rate and prevented mortality. As shown by experiments with ^{75}Se, silver interfered with selenium absorption (when given orally or i.m.) and allowed accumulation of a nontoxic selenium compound in the tissues, whereas copper provided primarily the latter effect. Presumably, because of their greater water insolubility, these nontoxic compounds are the selenides (Jensen, 1975).

Selenium-vitamin E deficiency symptoms were also induced in 20 ducklings fed an adequate diet supplemented with 0.2 percent silver acetate for three weeks. The birds showed anorexia, retarded growth, a reluctance to stand, and eventual fatalities (2 of the 18 ducklings affected) with myopathies in the gizzard, intestine, skeletal muscle, heart, and hydropericardium unless the diet was supplemented by 200 IU/kg of α-tocopherol. Selenium (0.0001 percent) as sodium selenite did not protect against the deficiency symptoms (Van Vleet, 1977).

Peterson, et al. (1973) fed 21 turkey poults a diet containing 0.09 percent silver as silver nitrate for four weeks, which significantly reduced body weight gain, hemoglobin, packed cell volume of the blood, and aortic elastin content while significantly increasing the ratio of wet heart weight to body weight. The heart enlargement was due to copper deficiency.* (Copper is part of the enzyme amine oxidase, required for elastin synthesis). Although six of the poults died (28.6 percent mortality) within the next 18 weeks, during which time they no longer received silver, the factors affected by silver nitrate had reverted to normal except for the appearance of the hearts. They were grossly enlarged, blunt at the apex, and showed marked dilation and thinness of the right ventricle.

Extending the report of the studies on turkey poults by Peterson, et al. (1973), Jensen, et al. (1974) found that there was a variable incidence of gizzard musculature degeneration, which was prevented by adding 0.0001 percent selenium or 50 International Units (IU) vitamin E per kg to the diet. These agents, however, did not affect the macrocytic hyperchromic anemia; but 0.005 percent copper in the diet reversed the anemia as was mentioned above.

Hoekstra (1975) enumerated some of the defects related to selenium deficiency in many animal species: fetal death and resorption; testicular and liver necroses; degeneration of kidney, muscle, and vessels; hemorrhage; and erythrocyte hemolysis. He proposed a metabolic scheme interrelating the effects of glutathione peroxidase and vitamin E as protectors against sulfur-containing amino acids, oxidant stressors, etc.; but the mechanism whereby silver interferes with selenium and glutathione peroxidase was not explained.

---

*Jensen, et al. (1974) later reported that giving the poults 0.005 percent copper in the diet reversed silver's effects on growth rate, blood, and cardiac tissue.

Rotruck, et al. (1973) found that there are four selenium atoms per molecule of the enzyme glutathione peroxidase. Noguchi, et al. (1973, both reports cited by Peterson and Jensen, 1975b) advanced the hypothesis that the selenium-containing glutathione peroxidase destroys peroxides and hydroperoxides within the extramitochondrial water-soluble fraction of the capillary cells and that lipid-soluble vitamin E prevents auto-oxidation of the lipids within the membrane* itself. The greater efficiency of vitamin E rather than selenium in curing selenium-vitamin E deficiency symptoms in silver-fed animals may be due to the fact that vitamin E acts directly, whereas selenium must first be synthesized into glutathione peroxidase or its metabolism and/or absorption are directly interfered with by silver (Peterson and Jensen, 1975b).

Teratogenicity

Few associations between silver and birth defects have appeared in the literature, and one is apparently erroneous.

Kukizaki (1975) found only weak cytotoxic effects when silver-tin alloy powder was incubated in seawater with fertilized eggs or early embryos of the sea urchin, Hemicentrotus pulcherrimus. Metallic mercury, on the other hand, was not only very cytotoxic, the embryos were deformed. However, five hours after incorporation with the silver-tin alloy into a dental amalgam, even the cytotoxicity almost disappeared.

---

*Alterations to hepatocyte membranes were consistently seen early in silver feeding studies producing liver necrosis (Grasso, et al. 1969).

Silver was among the 54 elements whose salts were tested for toxicity to 4- and 8-day-old chick embryos, by Ridgway and Karnofsky (1952); but it was not among the nine elements (Tl, Cr, Pb, Co, B, As, Rh, Ba, and Se) whose salts produced abnormalities in embryonic development.

Robkin, et al. (1973) reported concentrations of silver (determined by neutron activation analysis) in dry liver tissue from 12 anecephalic fetuses (0.75 ± 0.15 mg/kg), nine premature infants (0.68 ± 0.22 mg/kg), 12 fetuses from therapeutic abortions (0.23 ± 0.05 mg/kg), and 14 fetuses from spontaneous abortions (0.21 ± 0.05 mg/kg). Mercury concentrations exhibited a similar pattern. The age of the tissue groups increased in the order of increasing mercury concentrations. The accumulation of mercury with age may have accounted for the differences, not a teratogenic effect. The authors felt more data from large sample sizes were needed to decide whether the silver anomaly was due to a teratogenic effect or was also due to accumulation with age.

Barrie (1976) described two rare cases of fibular aplasia in human infants from mothers whose intrauterine devices had remained in place during pregnancy. One mother had an intrauterine device (IUD) of German silver (the Grafenburg ring) the other, an IUD of polyvinyl acetate containing barium and copper additives (the standard Dalkan® shield). Barrie mistakenly stated that the first shield is mainly silver. According to Thrush, et al. (1968), German silver comprises only nickel, copper, and zinc.

Mutagenicity

Demerec, et al. (1951) studied mutational changes in *Escherichia coli* by the method of inducing back-mutations from streptomycin dependence to nondependence. Incubation with silver nitrate solutions of 0.000005 to 0.000100 percent for 3 to 25 hours allowed 4.3 to 84 percent survival of *E. coli* with 2.1 to 8.2 mutants per 10^8 bacteria after incubation compared with 2.3 to 8.6 mutants per 10^8 bacteria for control plates. Only the lowest concentration gave more mutants than were in the controls (4.8 versus 2.3 mutants per 10^8 bacteria). Thus, silver nitrate was deemed nonmutagenic.

Mutations tested for in *Micrococcus pyogenes* var. *aureus* strain FDA209 were resistant to penicillin and/or streptomycin. Clark (1953) found that a 0.000001 percent solution of silver nitrate (a concentration that gave the minimum killing action) apparently was not mutagenic in that the solution did not favor formation of antibiotic-resistant mutants in *Micrococcus aureus*. (In fact, the controls showed more mutants than the test solutions.)*

Nishioka (1975) used the method reported in 1972 by Kada, et al. for screening chemical mutagens. The method, named rec-assay, observes differential growth sensitivities to chemicals in wild and recombination-deficient strains of *Bacillus subtilis*. Chemicals more inhibitory for Rec$^-$ than for Rec$^+$ cells are suspected mutagens based on their ability to damage DNA. After exposure for 24 hours to 0.05 ml of a 0.05 M silver chloride solution (sic), both Rec$^+$ and Rec$^-$ cultures showed the same degree of inhibition.

---

*90 versus 179 for streptomycin-resistant mutants per million cells. 9 versus 40 for penicillin-resistant mutants per million cells.

Fox, et al. (1969) had suggested that silver sulfadiazine derived its antimicrobial activity from its ability to react with cellular DNA. Rosenkranz and co-workers had found that it does *in vitro* but not *in vivo*. McCoy and Rosenkranz (1978) found that silver sulfadiazine had no mutagenic activity in the Ames test, which examines the substance's ability to mutate histidine-requiring strains of *Salmonella typhimurium* to histidine independence. Although the *typhimurium* tester strains gave the usual response to known base substitution and frameshift mutagens in plate assays, usually fewer than 19 mutants per plate were observed with silver sulfadiazine. In suspension culture, the antimicrobial activity of silver sulfadiazine (1 mg/l) was clearly observed; but the relative number of mutants per 100 million viable cells varied little (7.7 to 10.3) with time, whereas another antimicrobial--2-(2,2-dimethylhydrazino)-4,5-nitro-2-furylthiazole--showed definite mutagenic potential, with 394 mutants per 100 million viable cells 80 minutes after addition of 0.5 mg/l.

Apparently, silver is a normal, if minute, constituent of DNA. Sabbioni and Girardi (1977) found 0.2 mg/kg silver in calf thymus DNA, but 0.015 mg/kg silver was in the blank. Elements present at the same level as silver, up to 1.2 mg/kg, were mercury, selenium, rubidium, and chromium. Elements present at 2 to 1,450 mg/kg were barium (8), manganese (16), iron (11.6), strontium (2.2), and zinc (1,450).

Von Rosen (1954) exposed germinated Pisum seeds with 1 cm rootlets to solutions of heavy metal compounds at 20°C and observed that the chromosome-breaking ability of the very active metal ions were in the following (decreasing) order: Tl, Cd, Cu, Os, Hg, Ag, Ti, Ta, Au, Pt, Cr, and Co. The concentration of the silver ions (probably as the nitrate as in Von Rosen, 1957) was of the order 0.0001 M. The ions of silver and gold produced swollen prophase cells, where the chromosomes were visible as long threads but were often greatly fragmented. Von Rosen (1957) remarked that the elements that were radiomimetically active in producing chromosome disturbances were those that can form strong complexes with protein constituents.

Carcinogenicity

Implanted foils and disks and injected colloidal suspensions of metallic silver have been found to produce tumors or hyperplasia in several studies. Yet the investigators almost always qualify their findings by suggesting the effect is due to the particular physical form of the metal, to its being an exogenous irritant, or to its lowering resistance because of the presence of some solubilized silver ions. Some of the literature data are summarized in Table 17. The data included are of uneven quality because a few of the original references have not been located and some listings are

TABLE 17

Silver Tested for Carcinogenicity

Investigators	Animal	Strain or Type	Sex	Preparation and Dose	Site and Route	Animals with Tumors	Survival	Duration of Experiment
				Silver Nitrate				
Saffiotti & Shubik, 1963	20 mice[a]	Swiss	M	10% in distd. water 2/week for 43 weeks starting 1 week after topical application of 1.5% DMBA (7,12-dimethylbenz(a)anthracene) in mineral oil	Hair-free skin, topical	3 with 8 papillomas[b] (average latent period 19 weeks) 0 carcinomas	18 at 10 weeks 13 at 20 weeks	44 weeks,
Saffiotti & Shubik, 1963	20 mice[a]	Swiss	M	Same as above, except croton oil was substituted for the first silver nitrate treatment	Hair-free skin, topical	6 with 14 tumors (1 was a carcinoma) (average latent period 21 weeks)	19 at 10 weeks 15 at 20 weeks	44 weeks
Frei & Stephens, 1968	30 mice	Swiss inbred	M	10% in distd. water, 2/week for _ 50 days	Top ears, topical	0[c]	25 survivors	50 days
				Metallic Silver				
McDonald & Huffman, 1955 cited in Shubik & Hartwell, 1969	13 rats	Long Evans	M		Implanted in bladder	P		8 weeks
Nothdurft, 1955	Mice			Disks 12 x 0.02 mm 12/animal	Implanted 6 s.c. on back, 4 i.p., 2 s.c. on abdomen	P		9 to 12 months
Nothdurft, 1955	Rats	Wistar		Disks 17 x 0.02 mm 12/animal	Implanted 6 s.c. on back, 4 i.p., 2 s.c. on abdomen	2 sarcomas		9 to 12 months
Nothdurft, 1956 cited in Shubik & Hartwell, 1969	84 rats			17-mm disk implanted (8/animal)	s.c.	65 sarcomas		23 months

TABLE 17 (Continued)

Investigators	Animal	Strain or Type	Sex	Preparation and Dose	Site and Route	Animals with Tumors	Survival	Duration of Experiment
Oppenheimer, et al. 1956	25 rats	Wistar	M	2 pieces of foil, 1.5-cm wide	Imbedded, s.c., abdominal wall	14 (32%) (fibrosarcomas at site of imbedding)		275 to 625 days
Nothdurft, 1958	35 rats	Wistar	M & F	Fragments 1 x 1 x 0.02 mm	s.c.	0	24 at 18th month, 31 at 12th month	At most 33 months
Schmahl & Steinhoff, 1960	31 rats	BD		Colloidal silver suspension 1.75 mg. 4/week for 10 months then 2.5 mg/week for 7 months. Total dose 65 mg/rat	i.v. or s.c. injections	One spindle-cell sarcoma at injection site at 16 months. Later 8/26 (31%): 6 sarcomas, leukemia and a laminar epithelial carcinoma. (Average latent period 695 ± 150 days.)	(31%)[d]	17 months
Becker, et al. 1967	Rats			Platelets 11 mm x 3 mm thick	Implant	Malignancies at 295 days		295 days
Furst & Schlauder, 1977	Rats	Fischer-344		Fine powder (-300 mesh) in suspension in trioctanoin	s.c.	0[e]		

[a] Fifty female mice given only a similar initiating treating lived 20 to 140 weeks without developing tumors. Among control groups from the same colony, one of 240 females observed for their lifespan developed a papilloma that regressed; and of 240 males, there developed one skin papilloma and a carcinoma of skin appendages. Other control groups totalling 400 mice of both sexes did not develop any tumors within 100 weeks.

[b] The investigators judged silver nitrate to be an agent causing marked epidermal hyperplasia.

[c] John I Thompson and Company (1969), reported that the treatment induced 100% epithelial hyperplasia. It did not. It was therefore, not used in further studies of tumor promotion wherein 1.50% DMBA was used as the carcinogen. In the test described above, the only untoward effect reported was the presence of 17 inflammatory cells after 10 days in a standard area of ear epidermis, compared with three in the controls while the known tumor promoter 50% croton oil caused 176 inflammatory cells.

[d] The rate of spontaneous malignant tumor formation was 1 to 3% in 700 untreated rats.

[e] Rats injected with the vehicle or a suspension of gold powder developed one fibrosarcoma per group. By contrast, 60% of rats injected with cadmium powder developed fibrosarcomas at the injection site.

from "Substances Which Have Been Tested for Carcinogenicity"* (Hartwell, 1951; Thompson and Co., 1969; Shubik and Hartwell, 1969).

Furst (Chemical and Engineering News, 1975), in an address to orthopedic surgeons in West Germany, stated that the metals he and others had tested for carcinogenicity, silver, gold, copper, iron, and lead, were "benign."

Nothdurft (1958) found no difference in the incidence of sarcoma formation initiated by s.c. or i.p. injections of silver (17-mm diameter round disks) in rats and mice and that initiated by gold, platinum, or ivory. Wistar rats of both sexes were treated with pieces of cut-up silver foil (8 s.c. implants in each of 31 to 35 animals); largest particle size (1 x 1 mm) was observed for periods up to a lifetime. Similar implants of gold and platinum were made. After 12 months, there were 31 survivors in the silver group, 28 in the gold group, and 26 in the platinum group. The number of survivors after 18 months were 24, 19, and 20, respectively. One rat from each group was observed for 29 months. The last animal to die (at 33 months) had been treated with silver. None of the rats developed sarcomas.

---

*Some of the studies that have been listed in "Substances Which Have Been Tested for Carcinogenicity" were not really carcinogen assays at all. For example, Hanzlik and Presho (1923) inserted 0.53, 0.621, and 1.56 g silver granules in the gizzards of three pigeons and observed weight loss and sickness in the two pigeons receiving the lower doses. They recovered within 18 and 48 days, respectively. There was no histopathological examination of tissues. In another inappropriately included study, O'Connor (1954), supported by the British Empire Cancer Campaign, induced deep necrosis of the colon tissues by anal insertion into mice of silver nitrate crystals. The mucous membranes and muscle were examined for the extent of regeneration.

Oppenheimer, et al. (1956) imbedded two 1.5 cm circles or squares of silver foil s.c. into the abdominal wall of each of 25 male Wistar rats immediately ventral to the fascia on either side. The latent period of tumor formation (all fibrosarcomas) in 14 of the rats (32 percent) was 275 to 625 days. The authors had earlier shown that the physical form of plastics played a role in carcinogencity, implants of plain plastics causing many more tumors than perforated film, fibers, or powders. The effect of smoothness may be operative also with metal implants since flexible steel, tantalum, and vitallium foils also produced tumors, in identical experiments, and crumbly tin foil did not. (There were no controls.)

Silver alloys were not considered in Table 17 because of the uncertainty of attributing any effect solely to silver. Fujita (1971) imbedded a solid 1 cm^2 plate of a dental silver-palladium-gold alloy s.c. in rats and found tumors (fibrosarcomas, fibroadenomas, and fibromas) in 7 of 14 animals. The incidence of tumors was only 1 in 13 when the plate was perforated.

However, in another study, implanted smooth pellets of a silver-based dental alloy* or pure gold for 5 to 90 days in the oral submucous membranes of rabbits and in the liver, testes, and femoral muscles of rats, were judged to be rather innocuous. The implants produced proliferation of connective tissue and a release of neutrocytes, monocytes, and histiocytes as the primary effects and secondarily produced fibroblasts. The effects of the implants

*70.02 percent silver, 24.70 percent palladium, 5.23 percent gold, and 0.03 percent copper.

in the rabbits were judged to be mild. Spermatogenesis was noted in the degenerative seminiferous tubules among the proliferated fibrotic stroma surrounding the alloy pellets. In the muscle, new connective tissue invaded the fiber bundles (Habu, 1968).

Both colloidal silver and silver nitrate have been reported to promote tumor growth. Intratumoral injections of colloidal silver in 40 rats appeared to stimulate cancer growth rather than inhibit it as did similar injections of colloidal platinum. In only one of the treated rats (2.5 percent) did the tumor heal compared with 5 of the 30 control rats (16.6 percent). (Colloidal platinum injections in 342 rats had given 14.0 to 50.0 percent healing compared with 0 to 38.0 percent healing in the controls) (Guyer and Mohs, 1933).

Four rats were given s.c. injections of colloidal silver on one side and colloidal platinum on the other. After two hours, the metals in the subcutaneous tissues were surrounded by profuse serous exudates and beginning leukocyte invasion. At 24 hours, both metals had initiated fibroblastic proliferation, which replaced the leukocytic exudation almost completely by 48 hours. Colloidal platinum induced a thicker, denser fibroblastic capsule, which may explain its inhibitive effect on cancers by walling them off and diminishing the oxygen supply. Irritant ionic silver was probably present because of the presence of a discoloration in the nearby tissue fluids by 24 hours, and degeneration of the adjacent striated muscle. The foreign body reaction around platinum particles was not accompanied by injury to normal tissue. Possibly, the promotion, by silver, of cancer growth is due to the production of an area of lowered tissue resistance that allows resistant cancer cells to grow freely (Guyer and Mohs, 1933).

Schmahl and Steinhoff (1960) induced tumors in rats with i.v. and s.c. injections of colloidal gold* or colloidal silver. (The LD_{50} for i.v. administration of colloidal silver in rats is 67 mg/kg. (The animals died within 20 to 24 hours with severe pulmonary edema). They administered 1.75 mg silver to 31 BD-strain rats for the first dose, which was followed at weekly intervals by 2.45 mg s.c. doses, so that the total dose per animal over the 10-month period was 44 mg. The group was then given 2.5 mg weekly doses i.v. for seven months for an additional total dose of 65 mg Ag per rat. Argyria was noticeable in the skin and mucous membranes after 6 to 8 weeks, but their health and growth were not affected. Sixteen months after the start of the injections, one rat developed a spindle-cell sarcoma at the injection site. There were only 26 survivors at this time. Seven others later developed malignant tumors. Altogether, six sarcomas occurred at the injection site. Leukemia and lamellar epithelial carcinoma at the maxillary angle were also observed. The frequency of occurrence of malignancies in the survivors was 8/26 or 31 percent; 23 percent for the local malignancies. The average latent period was 695 ± 150 days. In 700 untreated rats, the rate of spontaneous malignant tumor formation was 1 to 3 percent.

Saffiotti and Shubik (1963) treated the hair-free skin of 20 male mice with a 1.5 percent solution of the carcinogen DMBA (7,12-

---

*Found to be noncarcinogenic.

dimethylbenz(a)anthracene) in mineral oil. One week later, the mice were treated with a 10 percent aqueous solution of silver nitrate to determine its promoting activity. The silver nitrate solution was applied twice weekly throughout the rest of the 44-week experiment. At 10 weeks, there were 18 survivors; at 20 weeks, 13. Three mice developed eight papillomas (but no carcinomas) with an average latent period of 19 weeks. Silver nitrate was judged to be an agent causing marked epidermal hyperplasia. In another 44-week series, where croton oil was substituted for the first silver nitrate treatment, there were 19 survivors at 10 weeks; 15, at 20 weeks. Six mice of 20 developed tumors, one of which was a carcinoma. The average latent period was 21 weeks. Fifty female mice given only a similar initiating treatment lived at least 20 weeks (the test extended for 140 weeks). None of the animals bore tumors. Among control groups from the same colony, one of 240 females observed for their life span developed a papilloma that regressed; and of 240 males, there developed one skin papilloma and a carcinoma of skin appendages. Other control groups totaling 400 mice of both sexes did not develop any tumors within 100 weeks.

On the other hand, silver nitrate has been found in at least one study to be a tumor inhibitor. Taylor and Carmichael (1953) studied the effect of metallic salts (mainly chlorides) on the embryo and tumor (C_3H mouse mammary adenocarcinoma) of tumor-bearing eggs and on dba mouse sarcoma transplants in dba mice. When 0.3 mg aqueous $AgNO_3$ was injected into the egg membrane (46 eggs), survival (at 3 days) was 91 percent that of the controls;

tumor weight, 79 percent; and embryo weight, 98 percent. Five consecutive daily subdermal injections of 1.0 mg silver nitrate in saline given to 14 dba mice bearing sarcomas in the inguinal area reduced the tumor size to 65 percent that of the controls (given only saline injections) at seven days, but reduced the body weight of the mice to only 96 percent. Silver nitrate was one of the more effective tumor growth inhibitors (along with the chlorides of Co, Cu, Hg, Ni, Rh, Ti, and Zn).

Although the literature is replete with clinical reports of cases of argyria, the connections between human cancers and silver as a causal agent are very tenuous. The following reports reflect the difficulty of finding even tenuous connections in the literature.

Schulze and Bingas (1968) attributed the formation of a meningioma surrounding a silver clip left from an operation two years before to remove an ependymoma in the brain of an 11-year-old girl to its action as a chronic exogenous stimulus. Hormonal changes during puberty caused the frequent recurrences of the ependymoma.

Some cases of esophageal cancer in certain areas of Brazil have been related to the assiduous habit of "drinking mate tea without sugar, in a gourd through a silver straw, at very hot temperature." According to Dantas (1975), the high temperature may be at least partly the cause of the esophageal cancer.

Bell, et al. (1952) reported that accidental incorporation of pieces of silver amalgam into the alveolus or gingiva during dental procedures appear as a grayish-blue macule in the oral mucous membrane. Unless subjected to stress, as when under a denture, they are not tender nor inflammatory. "They closely resemble a blue nevus and have been removed in some cases on suspicion of neoplasm." Under the microscope (low-power), "They at first glance give a strong impression of blue nevus." There was silver pigment in the blood vessels and a sparse sprinkle of histiocytes. "No giant cells, inflammatory infiltrates, or other tissue reactions have been seen."

CRITERION FORMULATION

Existing Guidelines and Standards

Both of the U.S. standards for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused argyria (Table 18). It should be pointed out how the minimum 1 g silver needed to produce argyria was determined. In their book, Hill and Pillsbury (1939) stated that only intravenous doses of silver could be used to determine accurately the amount of silver actually taken into the body since the extent of gastrointestinal or mucous membrane absorption was unknown. Silver arsphenamine had been administered i.v. to human patients suffering from syphilis; 19 of them (14 had advanced symptoms of syphilis; 11 had received other heavy metal treatment*) developed argyria. Those patients developing argyria had received total doses of silver ranging from 0.91 g to 7.6 g within 2 to 10 years. The average total dose was 2.3 g silver. (Fourteen of the patients developing argyria were males.) The total number of patients that had been treated with silver arsphenamine was not estimated, but they were probably quite numerous.*

Until the U.S. Public Health Service Drinking Water Standards of 1962 [U.S. Department of Health, Education and Welfare (DHEW), 1962], there were no restrictions on silver in drinking water.

---

*Hill and Pillsbury (1939) had pointed out that, "Generalized pigmentation of the skin resembling that of argyria may be seen following the introduction of various metals, in particular bismuth, arsenic, and gold." Eight of the 19 people had also received bismuth.

TABLE 18

Existing Standards Regarding Silver

Medium	Silver Concentration	Authority
Drinking water	50 µg/l	U.S. EPA, 1976; NAS, 1977
Drinking water	0.5 µg/l	State of Illinois (cited in NAS, 1977)
Drinking water	10 µg/l	State of California (cited in NAS, 1977)
Workplace air, threshold limit value, 8-hour time-weighted	0.01 mg/m^3	OSHA, 1974 (40 CFR 1910.1000)
Short-term exposure limit (15 minutes 4 times per day)	0.03 mg/m^3	ACGIH, 1977

Neither the World Health Organization International Standards of 1958 nor the European Standards of 1961 set a limit for silver in drinking water (McKee and Wolf, 1963).

The 1976 National Interim Primary Drinking Water Regulations (U.S. EPA, 1976) included a section on silver that is practically identical to the 1962 Drinking Water Standards (DHEW, 1962). Both begin, "The need to set a water standard for silver (Ag) arises from its intentional addition to waters for disinfection." Both state, ". . . the amount of silver from injected Ag-arsphenamine, which produces argyria, is precisely known. This value is any amount greater than 1 g of silver, 8 g Ag-arsphenamine." The condition to be avoided was argyria. The phraseology "any amount" is misleading, since probably hundreds of patients over at least two decades of this treatment for syphilis had received total doses of silver greater than 0.91 g (Hill and Pillsbury, 1939). The two documents acknowledge, however, that there is "considerable variability in predisposition to argyria," which is clearly seen upon examination of Hill and Pillsbury's report of a few hundred case histories from the literature.

The 1976 document omits the calculations from the 1962 document: "Assuming that all silver ingested is deposited in the integument, it is readily calculated that 10 μg/l could be ingested for a lifetime before 1 g silver is attained from 2 liters water intake per day; 50 μg/l silver could be ingested approximately 27 years without exceeding silver deposition of 1 g." Yet, both also consider that intake from foods is "60 to 80 μg/day," based on the balance study of Kehoe, et al. (1940), and that silver would be increased in sulfur-containing foods by combination with silver in the cooking water.

The National Academy of Sciences (NAS, 1977) in Drinking Water and Health made a somewhat different calculation: "The interim drinking water level of 50 µg/l would be equivalent to a retention of 50 ug of silver per day (on the assumption that 50 percent of the intake is retained in the body), and would result in an accumulation of 1 g in 55 years, to give a probable borderline argyria."

The U.S. National Aeronautics and Space Administration recommended silver at 100 µg/l for safely providing pure drinking water on space flights; Swiss health officials, 200 µg/l; and German health officials, 100 µg/l (Silver Institute, 1975).

Maximum contaminant levels for inorganic chemicals in the 1975 National Interim Primary Drinking Water Regulations (40 FR 59565) are based on an average consumption of 2 liters of water per day.

Current Levels of Exposure

Estimates of silver in human diets have varied widely -- from an average of 0.4 µg/day for three Italian populations (Clemente, et al. 1977) to 27 ± 17 µg/day (excluding water) in the United Kingdom (Hamilton and Minski, 1972) to 35 µg/day (man) and 40 µg/day (woman) (Tipton, et al. 1966), and 88 µg/day (Kehoe, et al. 1940). Snyder, et al. (1975) estimated the average intake of silver by man to be 70 µg/day based on a review of the literature. Some of these estimates were based on intake of both food and water. An estimate of 30 µg/day for the average human intake in food is reasonable.

Ambient air levels of silver up to 10.5 ng/m^3 would lead to intake of up to 0.24 ug silver per day (at 23 m^3 respired air per 24-hour period). Exposure from cigarettes is negligible.

An average value for silver ingestion by water intake cannot be made. Silver was detected in only 6.1 percent of 380 finished waters (and in only 6.6 percent of U.S. surface waters). Because of the recent increase of interest in water purification by silver in the United States, many people are probably ingesting water from nonpublic potable water sources at the 1962 drinking water limit of 0.05 mg/l. Shorter exposure of the U.S. population to European limits might occur during travel by plane or ship.

A diet high in seafood taken from silver-polluted water may increase daily silver consumption. Organisms serving as food for high trophic level aquatic species concentrate silver by a factor of about 200 (brown algae, 240; diatoms, 210). Other concentration factors in higher organisms of the food chain are mussels, 330; scallops, 2,300; oysters, 18,700; and North Sea marine organisms, average 22,000 (Cooper and Jolly, 1969). Thus, regular ingestion of fish, etc., from contaminated water might significantly increase silver dietary intake.

In the workplace, daily intake in the United States is limited to 100 µg/day (0.01 mg/m^3 x 10 m/^{3} per workday). Ground-based cloud-seeding generator operators, however, are exposed to air concentrations exceeding the maximum permissible concentration for several hours at a time.

Special Groups at Risk

People treated with silver-containing medicinals are most at risk of developing argyria, as demonstrated by Hill and Pillsbury (1939) who summarized 357 recorded cases of argyria, 89 percent of which were due to therapeutic use of silver. In the period 1931 to 1939, when more people were exposed to therapeutic forms of silver than in any previous period, 92 percent of the cases were due to medicinals. Cases of occupationally-caused argyria are seldom encountered in the recent literature and were usually diagnosed at least 30 years ago. Hobbyists (e.g., jewelry makers, photograph developers) may not be aware of the precautions needed with silver and may be more at risk of argyria.

There are large individual variations in silver absorption, retention, eliminations, and/or susceptibility to argyria. Although intravenous administration of a total of 0.91 to 7.6 g (average 2.3 g) silver as silver arsphenamine for 2 to 10 years has caused argyria, hundreds of patients have received up to 1.7 g silver i.v. as silver arsphenamine without developing argyria (Cooper and Jolly, 1969; Hill and Pillsbury, 1939).

Over 10,000 cases of burn and leg ulcer patients have been treated with silver medicinals. No cases of argyria have been reported, even when 0.5 percent silver nitrate was used and systemic absorption was shown.

Aside from argyria, more subtle effects may be due to silver ingestion. On the basis of animal experiments, people marginally deficient or deficient in copper, selenium, or Vitamin E may have their deficiency symptoms exacerbated. But rat studies did not support this suggestion. The possibility that silver might render iodine unavailable in regions that otherwise might have just enough iodine to prevent goiter is another suggested consequence of silver in drinking water (Boissevain and Drea, 1936). To support the contention, however, elevated silver concentrations had been found in the water of endemic goiter regions, such as the western slopes of the Colorado mountains (Boissevain and Drea, 1936).

Basis and Derivation of Criterion

The carcinogenic effect data reviewed in the document are not sufficiently conclusive to provide a quantitative carcinogenic risk assessment. No study demonstrating carcinogenicity of silver has met all of the criteria described in 40 CFR 162.11 (a) ii, A or 43 FR 163.83-2bc regarding appropriate route, chemical form, number of animals, histologic examination of organs, concurrently run control group, and all other quantitative parameters.

A review of the animal data showed that in 10 toxicologic experiments on chronic ingestion of drinking water by rats (rabbits included in one study), containing 50 to 20,000 µg/l ionic silver, no effects were observed in rats ingesting silver at 200 µg/l (Table 19), and further no significant toxic effects were observed at a dose level below 400 µg/l (Table 19). Initial physiological effects were suggested at doses of 400 to 500 µg/l of silver. If the no-observable-effect level (NOEL) of 200 µg/l (Just and Szniolis, 1936) is used in developing a criterion for silver, the following calculation could be made:

TABLE 19

Toxic Effects in Rats Chronically Exposed to Silver in Their Drinking Water

Silver Concentration (µg/liter)	Duration (months)	Effect	Reference
500	6-12	Increase in brain nucleic acids but not statistically significant. Significant increase in liver weight and RNA concentration at 6 months.	Kharchenko, et al. 1973a,b
2,000	12	Increase in brain nucleic acids (statistically significant for DNA). Significant increase in liver RNA concentration.	
20,000	6 12	Significant increase in brain nucleic acids. Significant decrease in brain RNA at 12 months.	
200	8	0	Savluk, 1973
2,000	8	Depression of absorption function of retinculoendothelial system.	
200	12	0	Savluk and Moroz, 1973
20,000	12	Changes in serum protein fractions and the composition of free amino acids.	
200	3.3	0	Just and Snziolis, 1936
400	3.3	Kidney hemorrhage.	

TABLE 19 (Continued)

Silver Concentration (µg/liter)	Duration (months)	Effect	Reference
700	3.3	More pronounced kidney changes.	
1,000	3.3	Kidney, spleen, and liver changes.	
50	5	No change in digestive organs.	Maslenko, 1976
20,000	5	Liver enzyme function changes. Growth depression by 36%. Pathomorphological changes in stomach, small intestine, and liver.	
100	4	0	Pak and Petina, 1973
20,000	4	Insignificant serum SH group depletion.	
50,000	4	Decreased serum SH.	

$$\frac{(0.2\ \text{mg/kg})\ (0.035\ \text{l/day})^{*}}{0.3\ \text{kg}^{**}} = 0.023\ \text{mg/kg/day}$$

0.023 mg/kg/day x 70 kg/adult human male = 1.6 mg/day

* Estimated volume of water consumed by rats.
** Estimated weight of one rat.

In accordance with The National Academy of Sciences guidelines (NAS, 1977), a safety factor of 100 would be applied to the NOEL to yield a concentration of 8 μg/l, i.e.:

$$\frac{1.6\ \text{mg/day}}{(100)\ 2\ \text{l}} = \frac{0.016\ \text{mg/day}}{2\ \text{l}} = 0.008\ \text{mg/l} = 8\ \mu\text{g/l}$$

A bioconcentration factor (BCF) has not been used in this derivation since the measured BCF for bluegill fish (U.S. EPA, 1978) is less than the concentration of silver in ambient water. It should be noted, however, that higher values have been reported for nonindigenous shellfish (Cooper and Jolly, 1969). A BCF relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of silver which might be ingested from the consumption of fish and shellfish. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). A measured BCF of less than 1.0 was obtained for silver using bluegills (U.S. EPA, 1978). For lack of other information, a value of 0.5 can be used as the weighted average BCF for silver and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans.

Although a theoretical "safe" level for ambient water would be derived from the animal data, the available reports from the literature are difficult to interpret due to a number of deficiencies, including the reported study by Just and Szniolis (1936). Histological details of the lesions are not described adequately. Experimental details, such as the number of animals used, are also not given. Therefore, the animal data do not provide sufficient grounds to formulate a sound criterion.

Ingestion of silver by humans results in the additive deposition (with no apparent elimination) of silver in skin and mucous membranes causing argyria. The current drinking water standard (USPHS) of 50 μg/l has been derived to protect against argyria. This standard assumes an accumulation of 1.0 g for the lowest effect over an exposure period of 55 years. The data used to derive this standard is obtained from the results of clinical studies reviewed by Hill and Pillsbury (1939) (see Table 14). Even though the NAS estimate is based on a somewhat shorter exposure period than the lifetime exposure used in the derivation of a criterion for ambient water quality, the NAS (1977) derived standard represents the best scientific judgement in extrapolating the shorter term human clinical and occupational evidence into long term (55 years) low level exposure from drinking water. The differences between the NAS standard and the ambient water quality criterion calculations is in the standard set of assumptions used in the extrapolation process from shorter term data to life span exposures. Since the NAS derived standard purports to protect the U.S. population against argyria through past experience, the 50 μg/l should be considered as the upper limit level for deriving the ambient water quality criterion, even though the calculated value based on the Hill and Pillsbury data for 70 years of human exposure would be somewhat lower (~20 µg/l). This criterion intends to protect humans against manifestation of argyria during lifetime exposure. It is fundamentally identical to that of NAS (1977) except that it considers exposure over a longer period of time.

To compare observed environmental level with the proposed criterion, silver has been detected at levels as low as 0.1 µg/l in 104 of 1,577 samples taken from 130 points in well and surface waters of the United States. The concentration in positive samples ranged from 0.1 to 38 µg/l with a median of 2.6 µg/l (Kopp, 1969). Silver concentrations in finished water from public water supplies have been found to be about 2.3 µg/l (Durfor and Becker, 1962; Kopp, 1969) with a maximum of about 6.0 µg/l, while the maximum detected in tap water supplies (2,595 samples) has been reported to be 30 µg/l (Taylor, 1971). Silver has been added in special applications to drinking water supplies at higher concentrations (up to 200 µg/l) as a disinfectant, but this method is not economically competitive for large public water supplies.

The animal toxicity data do not present compelling evidence to warrant changing the present standard of 50 µg/l accepted by NAS. This standard appears, through past experience, to be satisfactory to protect against argyria in humans. Given the limited precision of the 0.9 g argyria-inducing dose in humans, the adjustment of the NAS standard by correcting for lifetime (70 year exposure) does not seem to offer, in itself, a compelling reason to recommend a lower criterion. The maximum detectable silver concentration reported in water samples was 38 µg/l. (The median concentration reported, however, is 2.6 µg/l.) Assuming that 50 percent of the intake at this concentration is retained in the body (NAS, 1977), then it would require 65.6 years to retain the quantity believed to produce argyria, which is a conservative estimate. There have been no reported cases of argyria through ingestion at this level, and the current NAS standard appears to be protective. Therefore, the current NAS standard of 50 µg/l, which appears to be protective, is recommended as the ambient water quality criteria.

REFERENCES

Albright, C.G., et al. 1967. Development of an electrolytic silver-ion generator for water sterilization in Apollo spacecraft water systems. Apollo applications program. Final rep. Abstr. in Star 7, February 23, 1969.

American Conference of Governmental Industrial Hygienists. 1971. Documentation of the Threshold Limit Values for Substances in Workroom Air. 3rd ed. Am. Conf. Govt. Ind. Hyg., Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists. 1977. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1977. Am. Conf. Govt. Ind. Hyg., Cincinnati, Ohio.

Anania, T.L. and J.A. Seta. 1973. Industrial hygiene survey report. United States Mint, San Francisco, Calif. Natl. Inst. Occup. Safety Health.

Andelman, J.B. 1973. Incidence, Variability and Controlling Factors for Trace Elements in Natural, Fresh Waters. In: P.C. Singer (ed.), Trace Metals and Metal-organic Interactions in Natural Waters. Ann Arbor Sci. Publ. Inc., Ann Arbor, Michigan.

Andren, A.W., et al. 1974. Ecological Research. In: W. Fulkerson, et al. (eds.), Ecology and Analysis of Trace Contaminants. Progress rep. Oct. 1973 - Sept. 1974. Oak Ridge Natl. Lab., Oak Ridge, Tennessee. p. 61.

Anghileri, L.J. 1968. In vivo and in vitro deiodination of silver iodide. Experientia. 24: 895.

Anghileri, L.J. 1969. In vivo breakdown of insoluble halides. Acta Isotop. 9: 347.

Anghileri, L.J. 1971. Effects of the ligand on the biological behavior of chromium complexes: Their therapeutic possibilities as selective carriers. Int. Jour. Clin. Pharmacol. 4: 169.

Anspaugh, L.R., et al. 1971. Compilation of published information on elemental concentrations in human organs in both normal and diseased states. 2. Data summary ordered by atomic number, subordered by organs, suborgan, and general health state. Lawrence Livermore Lab., Univ. Calif., Livermore, Calif., UCRL-51013 Pt. 2. Natl. Tech. Inf. Serv., Springfield, Virginia.

Aponte, G.E. 1973. Some current concepts of the pneumoconioses. Ann. Clin. Lab. Sci. 3: 219.

Armour Research Foundation. 1952. Spectrographic study of meats for mineral-element content. Final rep. Natl. Livestock and Meat Board, Armour Res. Foundation of Illinois Inst. Tech., Chicago, Illinois.

Bader, K.F. 1966. Organ deposition of silver following silver nitrate therapy of burns. Plast. Reconstr. Surg. 37: 550.

Bala, Yu., et al. 1969. Age level of trace elements in the human body. Tr. Voronezh. Gos. Med. Inst. 64: 37; Chem. Abstr. 13: 96263u.

Bard, C.C., et al. 1976. Silver in photoprocessing effluents. Jour. Water Pollut. Control Fed. 48: 389.

Bargman, R.D. and W.F. Garber. 1973. The Control and Removal of Materials of Ecological Importance from Wastewaters in Los Angeles, CA, USA. In: S.H. Jenkins (ed.), Advances in Water Pollution Research. Proc. Sixth Int. Conf. in Jerusalem, June 18-23, 1972. Pergamon Press, New York. p. 773.

Barkov, G.D. and L.I. El'piner. 1968. O neobkhodimosti ogranicheniya kolichestva serebra v pit'evoi vode (The need for limiting the silver content of drinking water). Gig. Sanit. 33: 16.

Barrie, H. 1976. Congenital malformation associated with intrauterine contraceptive device. Br. Med. Jour. 1: 488.

Barsegyants, L.O. 1967. Differentsirovaniye vydelenii chelovecheskogo organizma putem emissionnogo spectral'nogo analiza (Discrimination of human excretions by emission spectrography). Sudebno-Med. Ekspertiza, Min. Zdravookhr. 10: 30; Chem. Abstr. 68: 5533.

Beattie, J.R. and P.M. Bryant. 1970. Quantitative safety analysis. II. Risk assessment. Nucl. Eng. De. 13: 240.

Becker, T., et al. 1967. Behavior of metallic foreign bodies in animals. Wiss. Chir.-Tag. Deut. Demokrat. Repub., 6th. 2: 1722; Chem. Abstr. 70: 76383t.

Bell, C.D., et al. 1952. Amalgam tattoo-localized argyria. Am. Med. Assoc. Derm. Syph. 66: 523.

Bienvenu, P., et al. 1963. Toxicite generale comparee des ions metalliques. Relation avec la classification periodique (General comparative toxicity of the metallic ions. Relation with the periodic classification). Compt. Rend. 256: 1043.

Bogen, J. 1974. Trace Element Concentrations in Atmospheric Aerosols and Rainwater, Measured by Neutron Activation and X-ray Spectrometry. In: Comparative Studies of Food and Environmental Contamination. Proc. Symp. Nucl. Techniques in Compar. Stud. of Food and Environ. Contam., Otaniemi, Finland, August 27-31, 1973. Int. Atomic Energy Agency, Vienna, Austria. p. 75.

Boissevain, C.H. and W.F. Drea. 1936. Relation between the occurrence of endemic goiter and the presence of traces of silver and barium in drinking water. Endocrinology. 26: 686.

Bondoc, C.C., et al. 1966. Metabolic effects of 0.5 percent silver nitrate therapy for extensive burns in children. Surg. Forum. 17: 475.

Bowen, H.J.M. 1966. Trace elements in biochemistry. Academic Press Inc., New York.

Boyle, R.W. 1968. Geochemistry of silver and its deposits with notes on geochemical prospecting for the element. Geol. Surv. Can., Bull. No. 160. p. 1.

Bradford, G.R. 1971. Trace elements in the water resources of California. Hilgardia. 41: 45.

Bradford, G.R., et al. 1968. Trace and major element content of 170 High Sierra lakes in California. Limnol. Oceanog. 13: 526.

Braidech, M.M. and F.H. Emery. 1935. The spectrographic determination of minor chemical constituents in various water supplies in the U.S. Jour. Am. Water Works Assoc. 27: 557.

Brar, S.S., et al. 1970. Instrumental analysis for trace elements present in Chicago area surface air. Jour. Geophys. Res. 75: 2939.

Browning, E. 1961. Toxicity of Industrial Metals. Butterworths. London.

Bruland, K.W., et al. 1974. History of metal pollution in southern California coastal zone. Environ. Sci. Technol. 8: 425.

Buckley, W.R. 1963. Localized argyria. I. Chemical nature of the silver containing particles. Arch. Dermatol. 88: 531.

Buckley, W.R. and C.J. Terhaar. 1973. The skin as an excretory organ in argyria. Trans. St. Johns Hosp. Dermatol. Soc. 59: 39.

Buckley, W.R., et al. 1965. Localized argyria. II. Chemical nature of the silver containing particles. Arch. Dermatol. 92: 697.

Bunyan, J., et al. 1968. Vitamin E and stress. VIII. Nutritional effects of dietary stress with silver in vitamin E-deficient chicks and rats. Br. Jour. Nutr. 22: 165.

Burke, J. 1973. Silver sulfadiazine cream in the treatment of burns. Aust. Jour. Hosp. Pharm. 3: 147.

Burton, R.M. 1970. The case of the mysterious tattoo. Jour. Dent. Child. 34: 114.

Camner, P., et al. 1974. Alveolar macrophages and 5 um particles coated with different metals. Arch. Environ. Health. 29: 211.

Camner, P., et al. 1977. Lung clearance of 4 um particles coated with silver, carbon, or beryllium Arch. Environ. Health. 32: 58.

Cannon, H. and H.C. Hopps. 1971. Environmental Geochemistry, Health and Disease. Geochemical Soc. of Amer., Inc. Boulder, Colorado.

Chemical and Engineering News. 1975. Screening of metal implants urged. Chem. Eng. News. 53: 20.

Chusid, J.G. and L.M. Kopeloff. 1962. Epileptogenic effects of pure metals implanted in motor cortex of monkeys. Jour. Appl. Physiol. 17: 697.

Clark, J. 1953. The mutagenic action of various chemicals on Micrococcus aureus. Proc. Okla. Acad. Sci. 34: 114.

Clemente, G.F., et al. 1977. Trace element intake and excretion in the Italian population. Jour. Radioanal. Chem. 37: 549.

Constable, J.D., et al. 1967. Absorption pattern of silver nitrate from open wounds. Plast. Reconstr. Surg. 39: 342.

Cooper, C.F. and W.C. Jolly. 1969. Ecological effects of weather modification: A problem analysis. School of Natural Resour., Univ. Mich., Ann Arbor, Michigan.

Cooper, C.F. and W.C. Jolly. 1970. Ecological effects of silver iodide and other weather modification agents: A review. Water Resour. Res. 6: 88.

Creasey, M. and D.B. Moffat. 1973. The deposition of ingested silver in the rat kidney at different ages. Experientia. 29: 326.

Curtin, G.C., et al. 1974/1975. Movement of elements into the atmosphere from coniferous trees in subalpine forests of Colorado and Idaho. Jour. Geochem. Explor. 3: 245.

Dams, R., et al. 1971. Quantitative relationships among the trace elements over industrialized N.W. Indiana. Proc. Symp. Nucl. Technol. Environ. Pollut. 1970: 139.

Dantas, W. 1975. Etiological and environmental factors (letter). Jour. Am. Med. Assoc. 231: 1338.

Dawson, G.W. 1974. The chemical toxicity of elements. BNWL-1815, UC-70. Battelle Pacific Northwest Lab., Richland, Washington.

Day, W.A., et al. 1976. Silver deposition in mouse glomeruli. Pathology. 8: 201.

Demerec, M., et al. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Nat. 85: 119.

Dequidt, J., et al. 1974. Etude toxicologique experimentale de quelques derives argentiques. 1. Localisation et elimination (Experimental toxicologic study of some silver derivatives. 1. Localization and elimination). Bull. Soc. Pharm. Lille. 1: 23.

Diplock, A.T., et al. 1967. Vitamin E and stress. III. The metabolism of D- -tocopherol in the rat under dietary stress with silver. Br. Jour. Nutr. 21: 115.

Diplock, A.T., et al. 1971. The effects of vitamin E on the oxidation state of selenium in rat liver. Biochem. Jour. 123: 721.

Dodds, E.C., et al. 1937. Prologation of action of the pituitary antidiuretic substances and of histamine by metallic salts. Lancet. 2: 309.

Dreisbach, R.H. 1963. Handbook of Poisoning. 4th ed. Lange Medical Publications, Los Altos, California.

Dulka, J.J. and T.H. Risby. 1976. Ultratrace metals in some enivornmental and biological systems. Anal. Chem. 48: 640.

Durfor, C.N. and E. Becker. 1962. Public water supplies of the 100 largest cities in the United States, 1962. U.S. Geol. Surv. Water Supply Paper 1812, U.S. Dept. Inter., U.S. Gov. Print. Off., Washington, D.C.

Durum, W.H. and J. Haffty. 1961. Occurrence of minor elements in water. Geol. Surv. Circ. 445, Washington, D.C.

Dutkiewicz, T., et al. 1978. Trace element content of human hair determined using neutron activation analysis as monitor of exposure effects to environmental metals. Chem. Anal. 23: 261.

Dymond, A.M., et al. 1970. Brain tissue reactions to some chronically implanted metals. Jour. Neurosurg. 23: 574.

Enders, A. and A. Moench. 1956. Silberelimination im Organismus bei experimentellar Argyrie (Silver elimination in experimental argyria). Arch. Exp. Pathol. Pharmakol. 229: 16; Biol. Abstr. 40: 3966.

Fedotov, D.D., et al. 1968. Effect of silver ions on the threshold of electroconvulsions. Tr. Gos. Nauch.-Issled. Inst. Psikhiat. 52: 281; Chem. Abstr. 71: 2016z.

Fleagle, R.G., et al. 1974. Weather Modification in the Public Interest. Am. Meteorol. Soc. and Univ. of Washington Press, Seattle, Washington.

Fox, C.L., Jr. 1973. Use of Silver Sulfadiazine in Burned Patients. *In*: J.B. Lynch and S.R. Lewis (eds.), Symp. on the Treatment of Burns. C.V. Mosby Co., St. Louis, Missouri. p. 123.

Fox, C.L., Jr. 1975. Silver sulfadiazine for control of burn wound infections. Int. Surg. 60: 275.

Fox, C.L., et al. 1969. Control of *Pseudomonas* infection in burns by silver sulfadiazine. Surg. Gynecol. Obstet. 128: 1021.

Frank, R.H., Jr. 1969. Trace metal pollution of the lower North Canadian River basin. Ph.D. dissertation. Univ. Okla. (Xerox Univ. Microfilms, Ann Arbor, Michigan.)

Frei, J.V. and P. Stephens. 1968. The correlation of promotion of tumor growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br. Jour. Cancer. 22: 83.

Fujita, S. 1971. Silver-palladium-gold alloys carcinogenicity and acid mucopolysaccharides in the induced tumors. Shika Igaku 34: 918; Chem. Abstr. 77: 136075a.

Furchner, J.E. and G.A. Drake. 1968. A radiation protection guide for silver-110 estimated from retention in small mammals. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3848-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 90.

Furchner, J.E., et al. 1966a. Retention of silver-110 by mice. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3610-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 186.

Furchner, J.E., et al. 1966b. Effective retention of silver-110 by dogs after oral administration. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3610-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 191.

Furchner, J.E., et al. 1968. Comparative metabolism of radionuclides in mammals. IV. Retention of silver-110m in the mouse, rat, monkey, and dog. Health Phys. 15: 505.

Furst, A. and M.C. Schlauder. 1977. Inactivity of two noble metals as carcinogens. Jour. Environ. Pathol. Toxicol. 1: 51.

Gafafer, W.M. (ed.) 1964. Occupational Diseases, a Guide to Their Recognition. U.S. Dept. Hlth. Edu. Wel., Pub. Hlth. Serv., U.S. Govt. Print. Off., Washington, D.C.

Gammill, J.C., et al. 1950. Distribution of radioactive silver colloids in tissues of rodents following injection by various routes. Proc. Soc. Exp. Biol. Med. 74: 691.

Ganther, H.E., et al. 1973. Protective Effects of Selenium Against Heavy Metal Toxicites. In: D.D. Hemphill (ed.), Trace Substances in Environmental Health. VI. Proc. Univ. Mo. 6th Annu. Conf. on Trace Subst. in Environ. Health, June 13-15, 1972. Columbia, Missouri. p. 247.

Garner, R.J. 1972. Transfer of radioactive materials from the terrestrial environment to animals and man. CRC Press, Cleveland, Ohio.

Garver, R.M. 1968. M.S. Thesis. San Diego State College, San Diego, California.

Grabowski, B.F. and W.G. Haney, Jr. 1972. Characterization of silver deposits in tissue resulting from dermal application of a silver-containing pharmaceutical. Jour. Pharm. Sci. 61: 1488.

Grant, G.C., et al. 1975. Lead, Mercury and Silver in Chilean Mummy Tissue. In: Int. Conf. on Heavy Metals in the Environ., Toronto, Ontario, Canada, Oct. 27-31, 1975. p. B-72.

Grasso, P., et al. 1969. The role of dietary silver in the production of liver necrosis in vitamin-E-deficient rats. Exp. Mol. Pathol. 11: 186.

Greenberg, R.R., et al. 1978. Composition and size distributions of particles released in refuse incineration. Environ. Sci. Technol. 12: 566.

Guyer, M.F. and F.E. Mohs. 1933. Rat carcinoma and injected colloidal platinum. Arch. Pathol. 15: 796.

Habu, T. 1968. Histopathological effects of silver-palladium-gold alloy implantation on the oral submucous membranes and other organs. Shika Igaku 31: 17; Chem. Abstr. 69: 95035b.

Ham, K.N. and J.D. Tange. 1972. Silver deposition in rat glomerular basement membrane. Aust. Jour. Exp. Biol. Med. Sci. 50: 423.

Hamilton, E.I. and M.J. Minski. 1972/1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. Sci. Total Environ. 1: 375.

Hamilton, E.I., et al. 1972/1973. The concentrations and distribution of some stable elements in healthy tissues from the United Kingdom. An environmental study. Sci. Total Environ. 1: 341.

Hansen, W.C., et al. 1966. Concentration and Retention of Fallout Radionuclides in Alaskan Arctic Ecosystems. In: Proc. Inter. Symp. Stockholm, 1966. Pergamon Press, Oxford. p. 233.

Hanzlik, P.J. and E. Presho. 1923. Comparative toxicity of metallic lead and other heavy metals for pigeons. Jour. Pharmacol. Exp. Ther. 21: 145.

Harker, J.M. and D. Hunter. 1935. Occupational argyria. Br. Jour. Dermatol. 47: 441.

Harrison, P. R., et al. 1971. Areawide trace metal concentrations measured by multielement neutron activation analysis. A one day study in northwest Indiana. Jour. Air Pollut. Contro. Assoc. 21: 563.

Hartford, C.E. and S.E. Ziffren. 1972. The use of 0.5 percent silver nitrate in burns: Results in 220 patients. Jour. Trauma 12: 682.

Hartwell, J.L. 1951. Survey of compounds which have been tested for carcinogenic activity. 2nd ed. Pub. Hlth. Serv. Publ. No. 149, Fed. Security Agency, Pub. Hlth. Serv., U.S. Govt. Print. Off., Washington, D.C.

Hawkes, H.E. and J.S. Webb. 1962. Geochemistry in Mineral Exploration. Harper and Row Publishers, Inc., New York.

Henderson, R.N. 1975. Silver sulfadiazine adverse effects. Am. Jour. Hosp. Pharm. 32: 1103.

Hill, C.H., et al. 1964. Mercury and silver interrelationships with copper. Jour. Nutr. 88: 107.

Hill, C.H. and G. Matrone. 1970. Chemical parameters in the study of *in vivo* and *in vitro* interactions of transtion elements. Fed. Proc. 29: 1474.

Hill, W.R. and D.M. Pillsbury. 1939. Argyria, the Pharmacology of Silver. The Williams and Wilkins Co., Baltimore, Maryland.

Hoekstra, W.G. 1975. Biochemical function of selenium and its relation to vitamin E. Fed. Proc. 34: 2083.

Hoey, M.J. 1966. The effects of metallic salts on the histology and functioning of the rat testis. Jour. Reprod. Fert. 12: 461.

Hunt, J.S., et al. 1976. Immune complex glomerular disease in argyric mice. Pathology. 8: 205.

Jenne, E.A., et al. 1977. Inorganic speciation of silver in natural waters - fresh to marine. Trans. Am. Geophys. Union. 58: 1168.

Jensen, L.S. 1975. Modification of selenium toxicity in chicks by dietary silver and copper. Jour. Nutr. 105: 769.

Jensen, L.S., et al. 1974. Inducement of enlarged hearts and muscular dystrophy in turkey poults with dietary silver. Poult. Sci. 53: 57.

Johnstone, R.T. and S.E. Miller. 1960. Occupational Diseases and Industrial Medicine. W.B. Saunders Company, Philadelphia, Pennsylvania.

Jones, A.M. and J.A. Bailey. 1974. Effect of silver from cloud seeding on cecal flora of rabbits. Water, Air, Soil Pollut. 3: 353.

Just, J. and A. Szniolis. 1936. Germicidal properties of silver in water. Jour. Am. Water Works Assoc. 28: 492.

Kalistratova, V.S., et al. 1966. Behavior of ^{111}Ag in animals. Raspredel. Biol. Deistvie Radioaktiv Izotop., Sb. Stratei. p. 146; Chem. Abstr. 67: 51853w.

Kehoe, R.A., et al. 1940. A spectrochemical study of the normal ranges of concentration of certain trace metals in biological materials. Jour. Nutr. 19: 579.

Kent, N.L. and R.A. McCance. 1941. The absorption and excretion of 'minor elements' by man. I. Silver, gold, lithium, boron and vanadium. Biochem. Jour. 35: 837.

Kent-Jones, D.W. and A.J. Amos. 1957. Modern Cereal Chemistry. 5th ed. The Northern Publishing Co., Ltd., Liverpool, England.

Kharchenko, P.D. and P.Z. Stepanenko. 1972. Characteristics of disturbances in albino rat higher nervous activity during the action of silver electrolytic solutions. Fiziol. Zh. Akad. Nauk. Ukr. RSR. 18: 596.

Kharchenko, P.D., et al. 1973a. Zmina vmistu nukleinovikh kislot u golovnomu mozku i pechintsi shchuriv pri trivalomu vvedenni ioniv sribla s pitnoyu vodoyu (Change in the nucleic acid level in rat brain and liver during long-term introduction of silver ions with drinking water). Fiziol. Zh. Akad. Nauk. Ukr. RSR. 19: 362.

Kharchenko, P.D., et al. 1973b. Izmenenie soderzhaniya nukleinovykh kislot v golovnom mozge pri dlitel'nom vvedenii ionov serebra s pit'evoi vodoi (Change in the nuclein acid content in the brain during long-term administration of silver ions in the drinking water). Vodopodgot. Ochistka Prom. Stokov. 10: 91.

Kiker, R.G., et al. 1977. A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children. Jour. Trauma. 17: 835.

Klein, D.A. 1978. Effects on Humans. In: D.A. Klein (ed.), Environmental Impacts of Artificial Ice Nucleating Agents. Dowden, Hutchinson, and Ross, Inc., Stroudsburg, Pennsylvania.

Klein, D.H. 1972. Mercury and other metals in urban soils. Environ. Sci. Technol. 6: 560.

Konradova, V. 1968a. The ultrastructure of the tracheal epithelium in rabbits following the inhalatin of aerosols of colloidal solutions of heavy metals. I. Changes in the ultrastructure of the tracheal epithelium after 2-hour inhalatin of colloidal solutions of iron and silver. Folia Morphol. 16: 258.

Konradova, V. 1968b. The ultrastructure of the tracheal epithelium in rabbits following the inhalation of aerosols of colloidal solutions of heavy metals. II. Signs of cell alteration in the epithelium after 8-hour inhalatin of colloidal solutions of iron and silver. Folia Morphol. 16: 265.

Kopp, J.F. 1969. The Occurrence of Trace Elements in Water. In: D.D. Hemphill (ed.), Trace Substances in Environmental Health -III. Proc. Univ. Mo. Third Annu. Conf. on Trace Subst. in Environ. Hlth., Univ. Mo., Columbia, Missouri., June 24-26, 1969. p. 59.

Kopp, J.F. and R.C. Kroner. 1967. Tracing water pollution with an emission spectrograph. Water Pollut. Contr. Fed. 39: 1660.

Kopp, J.F. and R.C. Kroner. 1970. Trace metals in waters of the United States. U.S. Dept. Inter., Fed. Water Pollut. Contr. Adm., Cincinnati, Ohio.

Kroner, R.C. and J.F. Kopp. 1965. Trace elements in six water systems of the United States. Jour. Am. Water Works Assoc. 57: 150.

Kukizaki, S. 1975. Studies on the effects of dental amalgam upon the fertilization and early development of sea urchin eggs (Hemicentrotus pulcherrimus). Jour. Jap. Soc. Dent. Appar. Mater. 16: 123.

Kul'skii, L.A., et al. 1972. Dinamika zmin korkovoi diya'nosti v bilikh shchuriv pri khronichnyi intoksikatsii sriblom (Dynamics of cortical acitivity changes in albino rats after chronic silver intoxication). Dopov. Akad. Nauk. Ukr. RSR, Ser. B. 34: 660.

Kul'skii, L.A., et al. 1973. Disinfection and Preservation of Water by Silver. In: Aktualne Vodoprovedeniye Sanitarniy Mikrobiologii. Med. Acad. USSR, Pub. Hlth. Water Inst., Moscow, USSR. p. 111; New Silver Technology: Silver abstracts from the current world literature. 1975. October. p. 11.

Lanford, C. 1969. Effect of trace metals on stream ecology. Paper presented at the Cooling Tower Inst. meeting, Jan. 20, 1969.

La Torraca, F. 1962. Reperti anatomo-isto-patologici ed istochimici nell'intossicazione acuta sperimentale da sali di argento (Anatomic, histopathological, and histochemical aspects of acute experimental intoxication with silver salts). Folia Med. 45: 1065; Chem. Abstr. 58: 11883f.

Leirskar, J. 1974. On the mechanism of cytotoxicity of silver and copper amalgams in a cell culture system. Scand. Jour. Dent. Res. 82: 74.

Lever, W. F. 1961. Histopathology of the Skin. J.B. Lippincott Co., Philadelphia, Pennsylvania.

Lifshits, V.M. 1965. Spectrographic determination of trace elements in fraction of erythrocytes and human plasma. Lab. Delo. p. 655; Chem. Abstr. 64: 3949b.

Luoma, S.N. and E.A. Jenne. 1977. The Availability of Sediment-bound Cobalt, Silver and Zinc to a Deposit-feeding Clam. In: H. Drucker and R.E. Wilding (eds.), Biological Implications of Metals in the Environment. Proc. 15th Annu. Hanford Life Sci. Symp. at Richland, WA, Sept. 29-Oct. 1, 1975. CONF-750929 Natl. Tech. Inf. Serv., Springfield, Virginia.

Marks, R. 1966. Contact dermatitis due to silver. Br. Jour. Dermatol. 78: 606.

Marshall, J.P. and R.P. Schneider. 1977. Systemic argyria secondary to topical silver nitrate. Arch. Dermatol. 113: 1077.

Martin, E.W. (ed.) 1965. Remington's Pharmaceutical Sciences. 13th ed. Mack Publishing Co., Easton, Pennsylvania.

Masironi, R. (ed.) 1974. Trace Elements in Relation to Cardiovascular Diseases. World Health Organ., Geneva, Switzerland.

Maslenko, A.A. 1976. Vliyanie serebyanoi vody i vody konservirovannoi serebrom na organy pishchevareniya (Effect of "silver water" and water preserved with silver on the digestive organs). Vrach. Delo. 5: 88.

Mazhbich, B.I. 1961. Some problems in pathogenesis of pulmonary edema provoked by silver nitrate. III. The mechanism of death of experimental animals. Bull. Exp. Biol. Med. 50: 821; Chem. Abstr. 55: 11657c.

McCabe, L.J. 1969. Trace metals content of drinking water from a large system. Presented at the Symp. on Water Qual. in Distr. Systems, Div. of Water, Air, and Waste Chem., Am. Chem. Soc. Natl. Mtg., Minneapolis, Minnesota. April 13, 1969.

McCabe, L.J. 1970. Metal levels found in distribution samples. Presented at the Am. Water Works Assoc. Seminar on Corrosion by Soft Water, Washington, D.C., June 21, 1970.

McCoy, E.C. and H.S. Rosenkranz. 1978. Silver sulfadiazine: Lack of mutagenic activity. Chemotherapy. 24: 87.

McDowell, L.R., et al. 1978. Influence of arsenic, sulfur, cadmium, tellurium, silver and selenium on selenium-vitamin-E deficiency in pig. Nutr. Rep. Int. 17: 19.

McKee, J.E. and H.W. Wolf (eds.) 1963. Water Quality Criteria. 2nd ed. Calif. State Water Resour. Contr. Board, Publ. 3-A (Reprint Jan., 1973).

Merritt, W.F. 1971. Identification and Measurement of Trace Elements in Fresh Water by Neutron Activation. In: Int. Symp. on Ident. and Measurement of Environ. Pollut., Ottawa, Ontario, Canada, June 14-17, 1971. Natl. Res. Coun. Canada, Ottawa, Canada. p. 358.

Mischel, W. 1956. Uber die chemische Zusammensetzung der menschlichen Plazenta mit besonderer Berucksichtigung des biogenen Amin Cholin (Chemical composition of the human placenta). Zentr. Gynakol. 78: 1089.

Mitteldorf, A.J. and D.O. Landon. 1952. Spectrochemical determination of the mineral-element content of beef. Anal. Chem. 24: 469.

Moffat, D.B. and M. Creasey. 1972. The distribution of ingested silver in the kidney of the rat and of the rabbit. Acta Anat. 83: 346.

Monafo, W.W. and C.A. Moyer. 1968. The treatment of extensive thermal burns with 0.5 percent silver nitrate solution. Ann. N.Y. Acad. Sci. 150: 937.

Moncrief, J.A. 1974. Topical antibacterial therapy of the burn wound. Clin. Plast. Surg. 1: 563.

Muroma, Ali. 1961. Skin reactions produced by certain metallic salts. Ann. Med. Exp. Biol. Fenniae. 39: 277.

Murthy, G.K. and U. Rhea. 1968. Cadmium and silver content of market milk. Jour. Dairy Sci. 51: 610.

Myers, A.T., et al. 1958. A spectrochemical method for the semiquantitative analysis of rocks, minerals, and ores. U.S. Geol. Surv. Bull. 1084: 207.

Nadkarni, R.A. and W.D. Ehmann. 1969. Determination of trace elements in the reference cigarette tobacco by neutron activation analysis. Radiochem. Radioanal. Lett. 2: 161.

Nadkarni, R.A., et al. 1970. Investigations on the relative transference of trace elements from cigarette tobacco into smoke condensate. Tobacco. 170: 25.

Nathanson, J.A. and F.E. Bloom. 1976. Heavy metals and adenosine cyclic 3,5-monophosphate metabolism. Possible relevance to heavy metal toxicity. Mol. Pharmacol. 12: 390.

National Academy of Sciences. 1977. Drinking Water and Health. U.S. Environ. Prot. Agency, Washington, D.C., PB-269 519. Natl. Tech. Inf. Serv., Springfield, Virginia.

Nelmes, A.J., et al. 1974. The Implication of the Transfer of Trace Metals from Sewage Sludge to Man. In: D.D. Hemphill (ed.), Trace Substances in Environmental Health - VIII. Proc. Univ. Mo. 8th Annu. Conf. on Trace Subst. in Environ. Hlth. Univ. Mo., Columbia, Missouri, June 11-13, 1974. p. 145.

Neri, L.C., et al. 1975. Health aspects of hard and soft waters. Jour. Am. Water Works Assoc. 67: 403.

Nesbitt, R.U. and B.J. Sandmann. 1977. Solubility studies of silver sulfadiazine. Jour. Pharm. Sci. 66: 519.

Newton, D. and A. Holmes. 1966. A case of accidental inhalation of zinc-65 and silver-110m. Radiat. Res. 29: 403.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185.

Noddack, I. and W. Noddack. 1939. Die Haufigkeiten der Schwermetalle in Meerstieren (The frequency of heavy metals in sea organisms.) Arkiv. Zool. 32: 1.

Nothdurft, H. 1955. Die experimentelle Erzeugung von Sarkomen bei Ratten und Mausen durch Implantation von Rundscheiben aus Gold, Silber, Platin oder Elfenbein (Experimental production of sarcomas in rats and mice by implantation of round disks of gold, silver, platinum, or ivory). Naturwiss. 42: 75.

Nothdurft, H. 1958. Uber die Nichtexistenz von 'Metallkrebs' im Falle der Edelmetalle (The non-existence of metal cancers in the case of noble metals). Naturwiss. 45: 549.

O'Conner, R.J. 1954. The healing of localized areas of necrosis in the colon of the mouse. Br. Jour. Exp. Pathol. 35: 545.

Olcott, C.T. 1948. Experimental argyrosis. IV. Morphological changes in the experimental animal. Am. Jour. Pathol. 24: 813.

Olcott, C.T. 1950. Experimental argyrosis. V. Hypertrophy of the left ventricle of the heart in rats ingesting silver salts. Arch. Pathol. 49: 138.

Oppenheimer, B.S., et al. 1956. Carcinogenic effect of metals in rodents. Cancer Res. 16: 439.

Orentreich, N. and H.H. Pearlstein. 1969. Traumatic tattoo due to silver salt. Arch. Dermatol. 100: 107.

Owens, C.J., et al. 1974. Nephrotic syndrome following topically applied sulfadiazine silver therapy. Arch. Intern. Med. 134: 332.

Page, A.L. 1974. Fate and effects of trace elements in sewage sludge when applied to agricultural lands. A literature review study (review copy). Ultimate Disposal Res. Prog., U.S. Environ. Prot. Agency, Cincinnati, Ohio.

Pak, Z.P. and V.P. Petina. 1973. Vliyanie serebra na aktivnost' SH-grupp syvorotki krovi belykh krys (Effect of silver on the activity of the sulfhydryl groups of white rat blood serum). Vodo-podgot. Ochistka Prom. Stokov. 10: 80.

Pariser, R.J. 1978. Generalized argyria. Clinicopathologic features and histochemical studies. Arch. Dermatol. 114: 373.

Peterson, R.P. and L.S. Jensen. 1975a. Interrelationship of dietary silver with copper in the chick. Poult. Sci. 54: 771.

Peterson, R.P. and L.S. Jensen. 1975b. Induced exudative diathesis in chicks by dietary silver. Poult. Sci. 54: 795.

Peterson, R.P., et al. 1973. Effect of silver-induced enlarged hearts during the first four weeks of life on subsequent performance of turkeys. Avian Dis. 17: 802.

Phalen, R.F. 1966. M.S. Thesis. San Diego State College, San Diego, California.

Phalen, R.F. and P.E. Morrow. 1973. Experimental inhalation of metallic silver. Health Phys. 24: 509.

Polachek, A.A., et al. 1960. Metabolism of radioactive silver in a patient with carcinoid. Jour. Lab. Clin. Med. 56: 499.

Putzke, H.P. 1967. Experimentelle Argyrose. (Schicksal der Silberablagungen in Leber und Pankreas) Experimental argyrosis. (The fate of silver deposits in liver and pancreas). Z. Ges. Inn. Med. 22: 48.

Ragaini, R.C., et al. 1977. Environmental trace metal contamination in Kellogg, Idaho, near a lead smelting complex. Environ. Sci. Technol. 11: 773.

Rattonetti, A. 1974. Determination of soluble cadmium, lead, silver, and indium in rainwater and stream water with the use of flameless atomic absorption. Anal. Chem. 46: 739.

Reynolds, C.L., Jr. and F.E. Warner. 1977. Experimental observations on the corrosion of silver-tin (Ag_3Sn) amalgams. Jour. Biomed. Mater. Res. 11: 629.

Ridgway, L.P. and D.A. Karnofsky. 1952. The effects of metals on the chick embryo: Toxicity and production of abnormalities in development. Ann. N.Y. Acad. Sci. 55: 203.

Robkin, M.A., et al. 1973. Trace metal concentrations in human fetal livers. Trans. Am. Nucl. Soc. 17: 97.

Roy, D.R. and J.A. Bailey. 1974. Effect of silver from cloud seeding on rumen microbial function. Water, Air, Soil Pollut. 3: 343.

Sabbioni, E. and F. Girardi. 1977. Metallobiochemistry of heavy metal pollution: Nuclear and radiochemical techniques for long term-low level exposure (LLE). Sci. Total Environ. 7: 145.

Saffiotti, U. and P. Shubik. 1963. Studies on promoting action in skin carcinogenesis. Natl. Cancer Inst. Monogr. 10: 489.

Sales L.A. and C.S. Duarte. 1960. Experimental study on the pathogenesis of acute pulmonary edema. I. Pulmonary edema induced by silver nitrate. Mal. Cardiovasc. 1: 39; Chem. Abstr. 56: 10801g.

Savluk, O.S. 1973. Vliyanie anodnorastvorimogo serebra na retikuloendotelial'nuyu sistemu eksperimental'nykh zhivotnykh (Effect of anodically dissolved silver on the reticuloendothelial system of experimental animals). Vodopodgot. Ochistka Prom. Stokov. 10: 72.

Savluk, O.S. and O.G. Moroz. 1973. Reaktsiya organizma belykh krys na dlitel'noe vvedenie serebra s pit'evoi vodoi (Reaction of albino rats to long-term intake of silver with the drinking water). Vodopodgot. Ochistka Prom. Stokov. 10: 99.

Sax, N.I. 1963. Silver--Silver Thioarsenite. In: Dangerous Properties of Industrial Materials. 2nd ed. Reinhold Publishing Corp., New York. p. 1174.

Schelenz, R. 1977. Dietary intake of 25 elements by man estimated by neutron activation analysis. Jour. Radioanal. Chem. 31: 539.

Schmahl, D. and D. Steinhoff. 1960. Versuch zur Krebserzeugung mit kolloidal Silber- und Goldlosungen an Ratten (Experimental carcinogenesis in rats with colloidal silver and gold solutions). Z. Krebsforsch. 63: 586.

Schulze, A. and B. Bingas. 1968. Meningioma development induced by a foreign body. Beitr. Neurochir. 15: 297.

Schwartz, L., et al. 1947. Occupational Diseases of the Skin. Lea and Febiger, Philadelphia, Pennsylvania.

Scott, K.G. and J.G. Hamilton. 1948. The metabolism of silver. Jour. Clin. Invest. 27: 555.

Scott, K.G. and J.G. Hamilton. 1950. The metabolism of silver in the rat with radiosilver used as an indicator. Univ. Calif. (Berkeley) Publ. Pharmacol. 2: 241.

Shaver, S.L. and K.E. Mason. 1951. Impaired tolerance to silver in vitamin E deficient rats. Anat. Rec. 109: 383.

Shaw, E.B. 1977. Questions need for prophylaxis with silver nitrate (letter). Pediatrics. 59: 792.

Shouse, S.S. and G.H. Whipple. 1931. Effects of intravenous injection of colloidal silver on haemopoietic system in dogs. Jour. Exp. Med. 53: 413.

Shubik, P. and J.L. Hartwell. 1969. Survey of compounds which have been tested for carcinogenic activity, Supplement 2. Pub. Hlth. Serv. Publ. No. 149, U.S. Dept. Hlth., Edu. and Wel., U.S. Govt. Print. Off., Washington, D.C.

Sill, C.W., et al. 1964. Comparison of excretion analysis with whole-body counting for assessment of internal radioactive contaminants. Health and Safety Div., AEC Accession No. 43318, Rep. No. IDO-12038. U.S. Atomic Energy Comm., Idaho Falls, Idaho.

Silver Institute. 1973a. Silver carbon filter purifies swimming pool. Silver Inst. Lett. 3: 1.

Silver Institute. 1973b. Silver clears up polluted water. Silver Inst. Lett. 3: 3.

Silver Institute. 1973c. Silver Institute board hears of new silver market. Silver Inst. Lett. 3: 1.

Silver institute. 1974. Silver purifiers at swimming pool show. Silver Inst. Lett. 4: 2.

Silver Institute. 1975. Silver guards good health. Silver Inst. Lett. 5: 1.

Silver Institute. 1976a. Filters with silver in planes, homes, offices. Silver Inst. Lett. 6: 2.

Silver Institute. 1976b. Silver: A $5 insurance policy. Silver Inst. Lett. 6: 1.

Silver Institute. 1976c. Tests show silver best water purifier. Silver Inst. Lett. 6: 1.

Silver Institute. 1977a. Silver in the healing of burns. Silver Inst. Lett. 7: 2.

Silver Institute. 1977b. Silver purifies water on drilling rigs. Silver Inst. Lett. 7: 1.

Silver Institute. 1977c. Silver compound saved legs marked for amputation. Silver Inst. Lett. 7: 3.

Silver Institute. 1978. In 70 countries silver cleans up polluted water. Silver Inst. Lett. 8: 1.

Skolil, L.L., et al. 1961. Whole body counter analysis of body burdens of silver-110 in humans. Sixth Ann. Meet. of Hlth. Physics Soc., Las Vegas, Nevada.

Smith, I.C. and B.L. Carson. 1977. Trace Metals in the Environment. Vol. 2. Silver. Ann Arbor Science Publishers, Inc., Ann Arbor, Michigan.

Snyder, W.S., et al. 1975. Report of the Task Group on Reference Man. Pergamon Press, Oxford.

Standler, R.C. and B. Vonnegut. 1972. Estimated possible effects of silver iodide cloud seeding on human health. Jour. Appl. Meteorol. 11: 1388.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stokes, P.M., et al. 1973. Heavy-metal tolerance in algae isolated from contaminated lakes near Sudbury, Ontario. Can. Jour. Bot. 51: 2155.

Strauch, B., et al. 1969a. Methemoglobinemia: A complication of silver nitrate therapy used in burns. AORN Jour. 10: 54.

Strauch, B., et al. 1969b. Successful treatment of methemoglobinemia secondary to silver nitrate therapy. New England Jour. Med. 281: 257.

Struempler, A.W. 1975. Trace element composition in atmospheric particulates during 1973 and the summer of 1974 at Chadron, NE. Environ. Sci. Technol. 9: 1164.

Sunderman, F.W., Jr. 1973. Atomic-absorption spectrometry of trace metals in clinical pathology. Human Pathol. 4: 549.

Swanson, A.B., et al. 1974. Antagonistic effects of silver and tri-o-cresyl phosphate on selenium and glutathione peroxidase in rat liver and erythrocytes. Federation Proc. 33: 693.

Taylor, A. and N. Carmichael. 1953. The effect of metallic chlorides on the growth of tumor and nontumor tissue. Univ. Texas Publ. No. 5314, Biochem. Inst. Stud. 5, Cancer Stud. 2. p. 36.

Taylor, F.B. 1971. Trace elements and compounds in water. Jour. Am. Water Works Assoc. 63: 728.

Thompson, John I. and Company. 1969. Survey of compounds which have been tested for carcinogenic activity, 1968-1969 volume. DHEW Publ. No. (NIH) 72-35, Pub. Hlth. Serv. Publ. No. 149. U.S. Dept. Hlth., Edu. and Wel., Washington, D.C.

Thrush, P.W., et al. 1968. A Dictionary of Mining, Mineral, and Related Terms. U.S. Dept. Inter., U.S. Govt. Print. Off., Washington, D.C.

Tipton, I.H. and M.J. Cook. 1963. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys. 9: 103.

Tipton, I.H. and P.L. Stewart. 1970. Long term studies of elemental intake and excretion of three adult male subjects. Dev. Appl. Spectrosc. 8: 40.

Tipton, I.H., et al. 1966. Trace elements in diets and excreta. Health Phys. 12: 1683.

Tong, S.S.C., et al. 1974. Trace metals in Lake Cayuga lake trout (Salvelinus namaycush) in relation to age. Jour. Fish. Fes. Board Can. 31: 238.

Toxic Materials News. 1975. EPA finds ocean dumping causing build-up of metals in some Maryland shellfish. Toxic Mater. News. 2: 24.

Toxic Materials News. 1978. Heavy metals pose no threat to Manassas water supply, Virginia says. Toxic Mater. News. 5: 4.

Turekian, K.K. and M.R. Scott. 1967. Concentrations of Cr, Ag, Mo, Ni, Co, and Mn in suspended material in streams. Environ. Sci. Technol. 1: 940.

U.S. Department of Health, Education, and Welfare. 1962. Public Health Service Drinking Water Standards. HEW Publ. 956. Washington, D.C.

U.S. EPA. 1976. National interim primary drinking water regulations. EPA-570/9-76-003. U.S. Environ. Prot. Agency, Off. of Water Supply.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, California. Final rep., Task II. Contract No. 68-01-3887.

Valente, P. and J.L. Axelrod. 1978. Acute leukopenia associated with silver sulfadiazine terapy. Jour. Trauma. 18: 146.

Van Campen, D.R. 1966. Effects of zinc, cadmium, silver and mercury on the absorption and distribution of copper-64 in rats. Jour. Nutr. 88: 125.

Vanselow, A.P. 1966. Chapter 26. Silver. In: H.D. Chapman (ed.), Diagnostic Criteria for Plants and Soils. Univ. Calif., Div. Agric. Sci., Riverside, California. p. 405.

Van Vleet, J.R. 1976. Induction of lesions of selenium-vitamin E deficiency in pigs fed silver. Am. Jour. Vet. Res. 37: 1415.

Van Vleet, J.R. 1977. Protection by various nutritional supplements against lesions of selenium-vitamin E deficiency induced in ducklings fed tellurium or silver. Am. Jour. Vet. Res. 38: 1393.

Vinogradov, A.P. 1953. The elementary chemical composition of marine organisms. Sears Foundation for Marine Research, Yale Univ., New Haven, Connecticut.

Von Rosen, G. 1954. Breaking of chromosomes by the action of elements of the periodical system and by some other principles. Hereditas. 40: 258.

Von Rosen, G. 1957. Mutations induced by the action of metal ions in Pisum. Hereditas. 43: 644.

Wagner, P.A., et al. 1975. Alleviation of silver toxicity by selenite in the rat in relation to tissue glutathione peroxidase. Proc. Soc. Exp. Biol. Med. 148: 1106.

Wahlberg, J.E. 1965. Percutaneous toxicity of metal compounds. A comparative investigation in guinea pigs. Arch. Environ. Health 11: 201.

Wall, F.E. 1957. Bleaches, Hair Colorings, and Dye Removers. In: E. Sagarin (ed.), Cosmetics: Science and Technology. Interscience Publishers, Inc., New York. p. 479.

Wall, F.E. 1972. Bleaches, Hair Colorings, and Dye Removers. In: M.S. Balsam, et al. (eds.), Cosmetics: Science and Technology. 2nd ed. Interscience Publishers, Inc., New York. p. 279.

Warburton, J.A. 1969. Trace silver detection in precipitation by atomic absorption spectrophotometry. Jour. Appl. Meteorol. 8: 464; Chem. Abstr. 71: 523.

Weissman, R.V. 1975. Caution and restraint (letter). Jour. Am. Dent. Assoc. 91: 736.

West, H.D. and H. Goldie. 1956. Topical localization in mouse of radioactive silver oxide $(Ag^{111})_2O$ introduced by various routes. Proc. Soc. Exp. Biol. Med. 92: 116.

West, H.D., et al. 1950. In vivo localization of radioactive silver at predetermined sites in tissue. Am. Jour. Roentgenol. Radium Ther. 64: 831.

Whanger, P.D., et al. 1976a. Effects of selenium, cadmium, mercury, tellurium, arsenic, silver and cobalt on white muscle disease in lambs and effect of dietary forms of arsenic on its accumulation in tissues. Nutr. Rep. Int. 14: 63.

Whanger, P.D. 1976b. Selenium Versus Metal Toxicity in Mammals. In: Proc. Symp. on Selenium-Tellurium in the Environ., Univ. Notre Dame, May 11-13, 1976. Industrial Health Foundation, Inc., Pittsburg, Pennsylvania. p. 234.

Winell, M. 1975. An international comparison of hygienic standards for chemicals in the work environment. Ambio. 4: 34.

Wood, M. 1965. Silver nitrate and burns--cautionµµµ Ariz. Med. 22: 817.

Wyckoff, R.C. and F.R. Hunter. 1956. A spectrographic analysis of human blood. Arch. Biochem. 63: 454.

Wysor, M.S. 1975a. Antimalarials: Screening of (orally administered) silver sulfonamides against _Plasmodium berghei_. Chemotherapy. 21: 284.

Wysor, M.S. 1975b. Orally administered silver sulfadiazine--chemotherapy and toxicology in CF-1 mice--_Plasmodium berghei_ (malaria) and _Pseudomonas aeruginosa_. Chemotherapy. 21: 302.

Wysor, M.S. 1977. Administration of silver sulfadiazine and radioactive derivatives thereof. U.S. Pat. 4,020,150. April 26, 1977.

Yoshikawa, H. 1970. Preventive effect of pretreatment with low dose of metals on the acute toxicity of metals in mice. Ind. Health. 8: 184.

Zapadnyuk, V.I., et al. 1973. O biologicheskoi roli medi i serebra i vliyanii ikh na passivno-oboronitel'nuyu reaktsiyu belykh krys (Biological role of copper and silver and their effect on the passive defense reactions of white rats). Vodopodgot. Ochistka Prom. Stokov. 10: 91.

Zech, P., et al. 1973. Syndrome nephrotique avec depot d'argent dans les membranes basales glomerulaires au cours d'une argyrie (Nephrotic syndrome with silver deposits in the glomerular basement membranes during argyria). Nouv. Presse. Med. 2: 161.